

UNSTABLE T WAVES IN LEADS II AND III IN PERSONS WITH NEUROCIRCULATORY ASTHENIA

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INTRODUCTION

ALTHOUGH much has been written concerning the psychiatric and clinical aspects of neurocirculatory asthenia, there is only a meager number of contributions which refer to the electrocardiographic features of this disorder. Of these reports, most are concerned with distortions of the T wave in Leads II and III¹⁻⁴ but, with a single exception,⁴ the emphasis has been placed upon the appearance of such changes only when the electrocardiogram is obtained with the subject sitting^{1, 2} or standing.³ For this reason, these bizarre ventricular deflections have been ascribed either to a presumed electrical reorientation of the heart resulting from changing contacts between the heart and surrounding intrathoracic tissues^{1, 2} or, in spite of a lack of any correlated measurements to support the contention, to a diminution in coronary flow.³ In any event, in both of these views the basic importance of a concomitant asthenic habitus has been stressed; in the one case because it will allow a greater freedom of cardiac mobility,^{1, 2} and in the other because a congenitally small heart, which supposedly cannot maintain an effective coronary circulation during the readjustments to postural change, is always assumed to be associated with such a body build.³ However, since neither of these interpretations could be reconciled with the occurrence of similar alterations in the electrocardiograms of persons with functional derangements of the cardiovascular system when the record is made with the subject recumbent,^{4, 5} the authors undertook to explore other possible mechanisms which could account for these T-wave changes. The observations of Ewert⁶ and others,^{7, 8} which indicated that augmented adrenergic activity can be responsible for orthostatic T-wave modifications in Leads II and III in persons subject to syncope, suggested that a disturbance of normal vagosympathetic relationships might equally well be applied to explain, in cases of functional heart disease, comparable changes in records made with the subject standing, sitting, or recumbent. This consideration prompted a series of experiments by us in a group of patients with neurocirculatory asthenia. This report presents the results of such studies.

MATERIAL AND METHOD

Among a group of men originally referred to the hospital for a cardiovascular survey because of physical signs and/or symptoms suggestive of structural cardiac disease, 25 patients were selected for more detailed study because their electrocardiograms revealed T-wave changes in Leads II and III

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in the upright position alone or in both the recumbent and upright positions, in spite of the fact that no substantiating evidence of organic heart disease could be established during a suitable period of observation. Such a method of selection therefore excluded from the study those who exhibited any of the following stigmas: persistent elevation of the arterial blood pressure; persistent tachycardia; any type of cardiac arrhythmia other than a sinus arrhythmia; systolic cardiac murmurs which were not significantly modified by heart rate, postural change, and the respiratory phases; orthostatic hypotension; elevated erythrocyte sedimentation rate; an elevated basal metabolic rate; cardiac and/or aortic enlargement as estimated in the teleroentgenogram by generally accepted methods of cardiac mensuration.

The subjects ranged in age from 18 to 35 years. No one body type was consistently encountered; the asthenic, the hypersthenic, and the intermediate body builds occurred with about equal frequency. The presenting symptoms, not all of which appeared in every case, included nervousness, weakness, excessive perspiration, palpitation, dull or sharp left inframammary pain unrelated to exertion and usually associated with hyperesthesia over the precordium; aches in various joints without redness, swelling, or limitation of motion of these structures; dizziness; shortness of breath of the nonhyperventilation type and usually described as "a feeling as though not enough air can get into the lungs."

The cardiovascular apparatus was repeatedly scrutinized by the usual methods of physical examination. In addition, teleroentgenograms of the chest and erythrocyte sedimentation rate determinations were routinely obtained. In many instances the basal metabolic rate also was measured.

The electrocardiographic studies were performed in the following manner: on the day of admission a record, both in the recumbent and in the upright position, was obtained,* after the technician ascertained that the patient had not been smoking for at least thirty minutes prior to the time of the test. The leads employed were the three standard limb leads and precordial leads CF₄ and CR₁ taken according to the technique recommended by the American Heart Association. The chest position was carefully marked in order to exclude the possibility of malposition of the exploring electrode, a factor which might contribute to distortion of the T wave in the precordial lead.

On the following day, a set of tracings was again obtained and immediately inspected by one of us. If T-wave distortions were noted in Leads II and III in these records, electrocardiograms were made thirty and sixty minutes following the intravenous administration of 0.5 mg. of ergotamine tartrate (Gynergen)[†]; the technician made certain that the subject had abstained from smoking prior to and during the experiment.

*Previous experiments had indicated that the orthostatic effects upon the electrocardiogram which follow an active change of position were no different from those which followed tilting of the subject to an 80-degree angle with the horizontal, provided the patient did not sway excessively after assuming the upright position, and provided a short waiting period of two minutes was employed to allow for vascular readjustments. For this reason, both methods were interchangeably used.

[†]Previous clinical trials had indicated that the maximal sympathetolytic effects of ergotamine tartrate, when the drug is administered intravenously in a dosage of 0.5 mg., appear between thirty and sixty minutes after the injection and will last ninety minutes after the injection.

Of those patients whose records showed orthostatic T-wave distortions in Leads II and III, several were selected for an experiment in which the electrocardiographic changes which followed the Flack test could be observed. In the performance of this type of experiment, a continuous record of Lead II was obtained with the subject recumbent just prior to and during a period of forced expiration. The expiratory blast was maintained to the point of obliteration of the radial pulse and was of sufficient force to raise and maintain a column of mercury in the sphygmomanometer to a level of 40 millimeters.

In certain other instances in which orthostatic T-wave abnormalities had developed in Leads II and III, comparable records were obtained in the upright position before and after compression of both legs at the mid-thigh level. The compression was accomplished by snugly fitted pneumatic cuffs inflated to a pressure of 300 mm. of mercury and maintained at this level throughout the experiment. The pressure was applied while the patient was supine and after the legs had been elevated for a sufficient length of time to permit the blood in the superficial veins to drain off as much as possible. Localized bulging of the inflated cuff was prevented by the application of an elastic bandage around the cuff before it was inflated. When significant modifications of the orthostatic distortions resulted from this procedure, the experiment was repeated with compression of equivalent degree being applied just above each ankle.

Finally, in certain selected cases, the effects of amyl nitrite and atropine sulfate were tested separately. The electrocardiograms were made with the patient in the recumbent position, and the patient had abstained from tobacco prior to and during the testing period. A control curve having been obtained, the amyl nitrite was administered by inhalation from a freshly broken pearl containing 5 minims of the drug, after which the electrocardiographic effects were recorded in either a single lead or in multiple limb leads during the relatively brief period when flushing of the skin and tachycardia were maximal.*

The atropine sulfate was administered subcutaneously. Records were obtained forty to sixty minutes afterward. The dose employed was usually 2.5 mg.† dissolved in 2 c.c. of sterile water.

ANALYSIS OF DATA

In each of the 25 cases which form the basis for the present study, orthostatic distortions of the T wave accompanied by varying increments in the heart rate, appeared in Leads II and III. In each instance, the orthostatic T-wave abnormality was completely, or almost completely, abolished by the administration of a sympatholytic drug (ergotamine tartrate), and in five instances it was considerably modified by compression of the thighs. In 15 of these patients, changes analogous to those which resulted from the assumption

*The vaporized contents of a pearl of amyl nitrite containing 5 minims of the drug will reflexly excite sympathetic activity to a profound degree. These sympathicomimetic effects are maximal within thirty to sixty seconds after the inhalation of that amount of the drug, and completely disappear in two to three minutes.

†Previous trials had indicated that in order to ensure the vagoparetic action from atropine sulfate, the drug must be administered in this large dosage. When given hypodermically, the maximal effect will appear between forty and sixty minutes after its injection.

of the upright position were provoked by a sympathetico-mimetic drug (amyl nitrite) in the electrocardiogram made with the subject recumbent. In 10 instances, the T wave in Leads II and III of the electrocardiogram made in recumbency underwent varying degrees of modification following the administration of a vagoparetic drug (atropine sulfate). A similar effect followed the Flack maneuver in six instances. The data from five representative cases which have been selected for more detailed analysis will be separately reviewed.

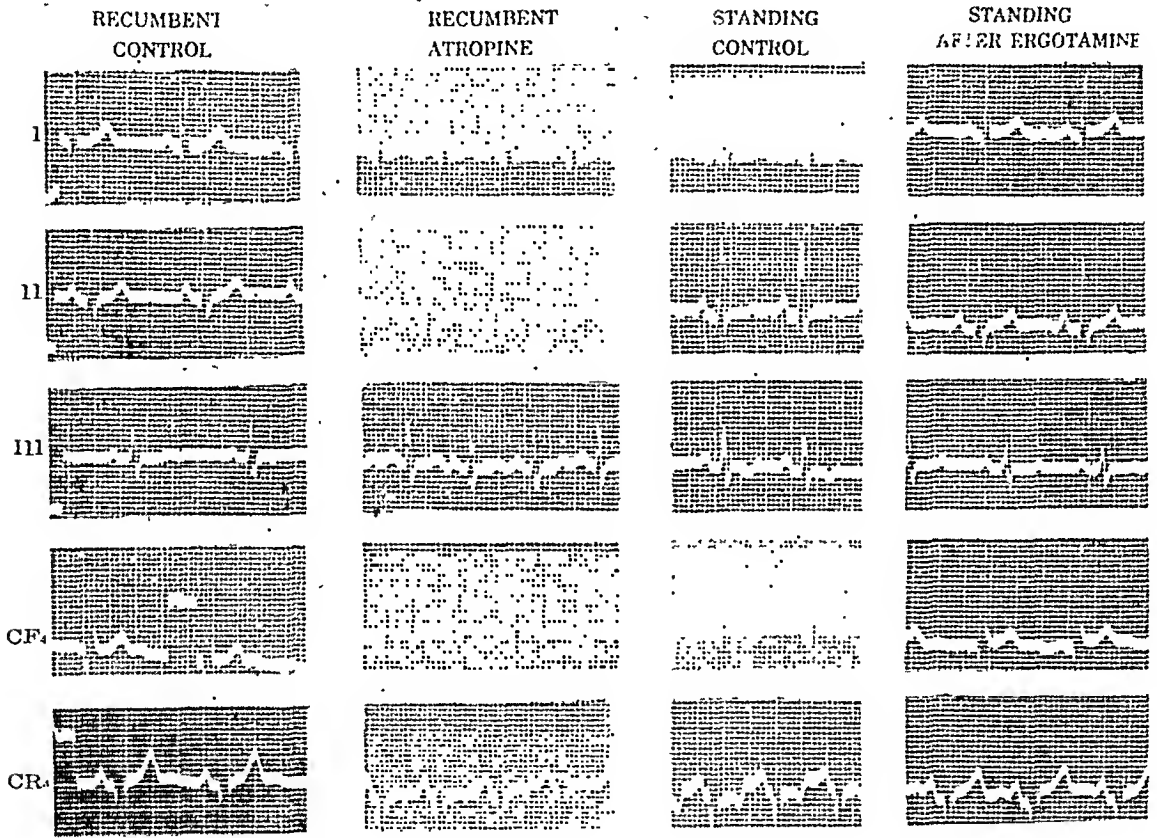


Fig. 1.—Case 1. The electrocardiogram is discussed in the text.

CASE 1.—1. Although the orthostatic T-wave distortions in Leads II and III were associated with some cardiac acceleration, an associated orthostatic tachycardia, in the strictest sense, had not developed. The heart rate with the patient in the recumbent position averaged 70 per minute and, in the upright position, 95 per minute (Fig. 1).

2. Although the heart rate with the patient in the recumbent position became more rapid after the administration of a vagoparetic drug than it had following the assumption of the upright position alone, significant T-wave distortions in Leads II and III developed only during the period of standing. On the other hand, the T-wave distortions in the precordial leads which developed in recumbency after atropine sulfate, and in the upright position before the drug was given, were comparable (Fig. 1).

3. A sympathetolytic drug (ergotamine tartrate) prevented orthostatic cardiac acceleration and also orthostatic T-wave distortions (Fig. 1).

Comment.—The orthostatic T-wave distortions in Leads II and III might conceivably be related to a shortening of the diastolic period which inevitably supervenes with an acceleration of the heart. Conversely, then, the prevention by means of ergotamine tartrate of these orthostatic effects upon the ventricular deflection might be presumed to be

due merely to a lengthening of the diastolic period which ensues with a reduction of the heart rate. This view cannot be arbitrarily denied, but it hardly seems applicable in this instance, since the configuration of the T wave in Leads II and III is not significantly modified by atropine sulfate, even though the cardiac acceleration which followed the administration of this vagoparetic drug exceeded that which resulted from the assumption of the upright position. An alternative concept, which immediately suggests itself as an explanation of this difference, is the possibility that an augmentation of sympathetic activity, physiologically provoked either by the assumption of the upright position or the administration of a vagoparetic drug, can accelerate the sinus rate (chronotropic effect) and independently modify the events associated with electrical systole (dromotropic effect).

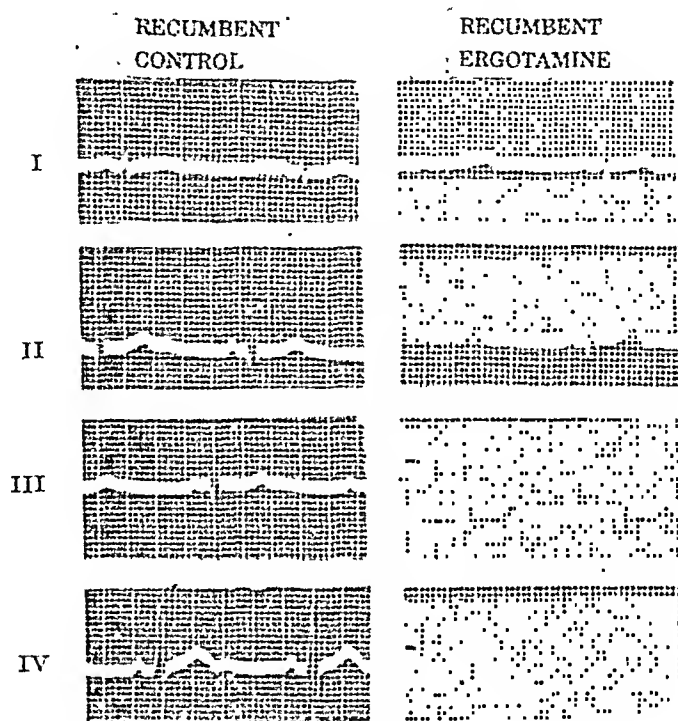


Fig. 2.—Case 3. The electrocardiogram is discussed in the text.

Following the administration of a sympathetolytic drug, such a distinction can apparently be made in some instances, the form of the T wave becoming modified without any significant change in the heart rate (Fig. 2). Therefore, the normalization of the ventricular deflection by ergotamine tartrate, when the electrocardiogram was made with the subject standing, might be ascribed not only to the decrement in the standing heart rate, but also to an inhibition by this drug of a dromotropic sympathetomimetic effect reflexly provoked by the upright position. In addition, this response of the T waves to the administration of ergotamine tartrate would seem to exclude a change in cardiac rotation as being responsible for the original orthostatic aberrations of the ventricular deflections.

CASE 2.—1. The maneuver of tilting the body upright to approximately 80 degrees did not result in a distortion of the T wave in Leads II and III unless a significant cardiac acceleration also developed (Fig. 3).

2. A sympathetolytic drug (ergotamine tartrate) prevented any significant orthostatic cardiac acceleration and also any orthostatic T-wave distortions (Fig. 3).

3. In the electrocardiogram made with the subject recumbent, T-wave changes in Leads II and III were provoked by the administration of amyl nitrite or atropine sulfate. These changes were of the same nature, if not necessarily of the same degree, as those which followed the assumption of the vertical stance (Fig. 3).

Comment.—The facts that orthostatic distortions of the T waves in Leads II and III occur only in association with cardiac acceleration and that such distortions can be prevented

by the use of a sympatheticolytic drug which also reduces the heart rate suggest that the abnormal form of the T wave is related either to the shortened diastolic period which results from the cardiac acceleration or to a mechanism which can provoke a sinus tachycardia as well as independently modify the events associated with electrical systole. The interpretation that the bizarre T wave is related to the increased heart rate per se would seem to be supported by the fact that, following the administration of amyl nitrite, changes identical with the orthostatic distortions occur in records made with the subject recumbent, provided that a comparable acceleration of the rate is provoked by this drug. On the other hand, the fact that the administration of atropine sulfate and of amyl nitrite produce

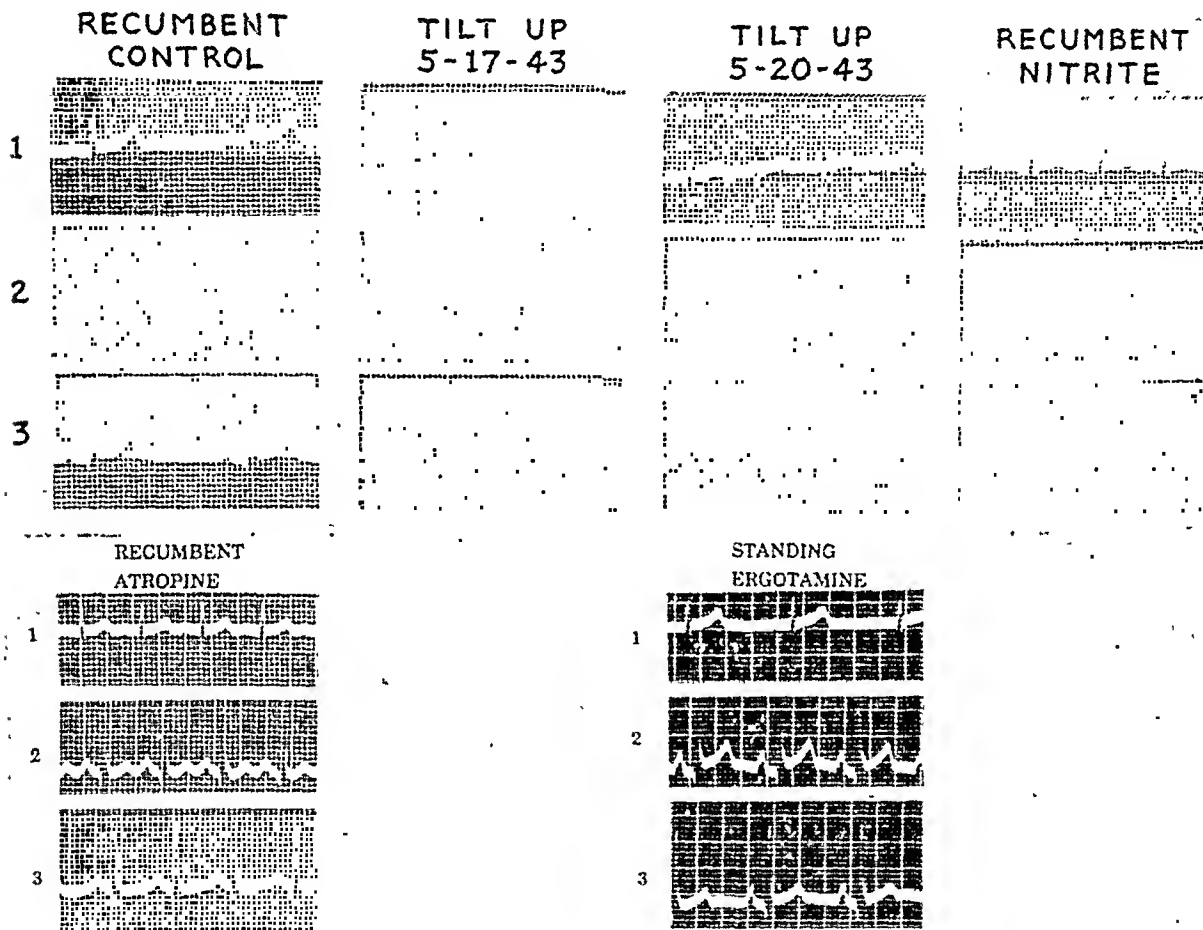


Fig. 3.—Case 2. The electrocardiogram is discussed in the text.

unequal degrees of T-wave modification, even though the tachycardia produced by these drugs is identical, would suggest that the tachycardia and the orthostatic T-wave changes represent separate chronotropic and dromotropic actions, respectively, of a sympathetico-mimetic effect. The differing dromotropic influences of atropine sulfate and amyl nitrite, in turn, can be predicated upon the fact that the latter drug is the more profound adrenergic stimulant in man.⁵ The orthostatic distortions of the T wave which develop in Leads II and III when there is an associated orthostatic tachycardia presumably are also an electrocardiographic expression of the dromotropic effect of heightened sympathetic activity, since they do not appear when the heart is under the influence of a sympathetico-lytic drug such as ergotamine tartrate. Also, this modifying influence of ergotamine tartrate, as well as the lack of any significant T-wave change when the upright position is unassociated with any significant cardiac acceleration, are undoubtedly strong evidence

against the opinion that increased cardiac mobility is responsible for orthostatic distortions of the ventricular deflections.

The likelihood that the original orthostatic distortions of the T wave are to be ascribed to impaired coronary flow would seem to be excluded by the normalizing effect of ergotamine tartrate since this drug is believed to produce also some constriction of the coronary arteries. Too, the marked distortion of the T wave in Leads II and III which followed the administration of a profound coronary dilator such as amyl nitrite indicates that a reduction in coronary flow is not a valid concept in attempting to explain T-wave changes which may occur in cases of neurocirculatory asthenia.

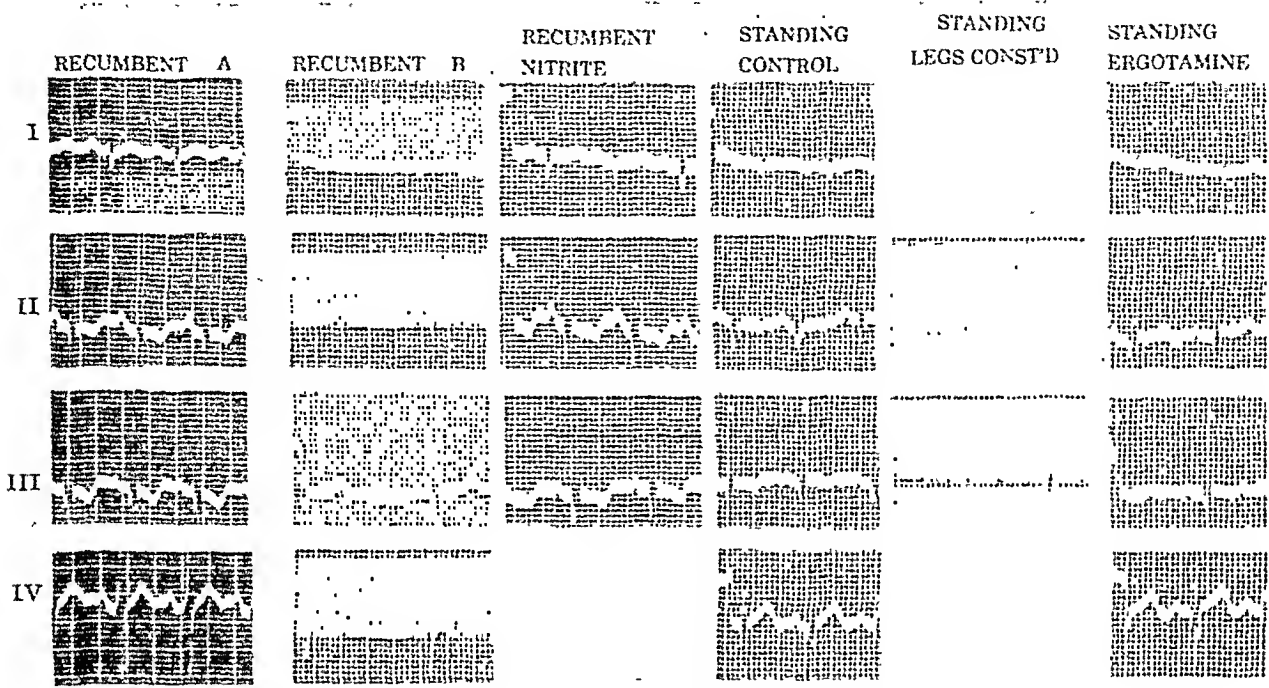


Fig. 4.—Case 3. The electrocardiogram is discussed in the text.

CASE 3.—1. During a febrile period, the electrocardiogram made with the subject recumbent revealed the presence of a sinus tachycardia with a heart rate of 130 per minute and concomitant inversion of the T wave in Leads II and III (Fig. 4).

2. During an afebrile period, the electrocardiogram made with the subject recumbent revealed the presence of a sinus rate of 60 per minute and T waves in Leads II and III of normal amplitude and configuration (Fig. 4).

3. Distortions of the T wave in Leads II and III occurred when the electrocardiogram was made with the subject recumbent, immediately following the inhalation of amyl nitrite. These changes in the ventricular deflection were associated with an increase in the sinus rate to 125 per minute (Fig. 4).

4. Distortions of the T wave in Leads II and III followed the assumption of the upright position alone. These changes in the ventricular deflection were associated with an equally significant increment in the heart rate and were abolished either by constriction of the thighs or by the administration of ergotamine tartrate, both of which procedures resulted in a reduction in the orthostatic heart rate to approximately 100 beats per minute (Fig. 4).

Comment.—In records made with the subject recumbent, T wave distortions in Leads II and III occurred spontaneously during a febrile period or were provoked, when no fever was present, by the inhalation of amyl nitrite. Since these changes are analogous to those which followed the assumption of the upright position, the possibility is suggested that a similar mechanism is operative in these modifications of the ventricular deflections. Inasmuch as cardiac acceleration is a concomitant occurrence in all these circumstances, it might be presumed that the tachycardia alone, with its resultant shortening of the diastolic period, might be the factor responsible for the altered shape of the T wave.

On the other hand, it seems to be equally plausible to relate both the tachycardia and the bizarre T waves to the separate chronotropic and dromotropic effects, respectively, of heightened sympathetic activity provoked either by the fever, the amyl nitrite, or the vertical stance. In this particular case, such an interpretation is especially applicable, since on another occasion, in a record made with the subject recumbent, the administration of a sympathetolytic drug was followed by a significant modification in the T waves without any alteration of the heart rate (Fig. 2). It is also noteworthy that either ergotamine tartrate or constriction of the thighs considerably modified the orthostatic distortion of the T waves in Leads II and III. Although this effect was presumably achieved by these procedures because of their inhibitory influences upon reflex sympathetic excitation, the mode of action is undoubtedly dissimilar. In the former instance a pharmacologic barrier between sympathetic fibers and end organs in the heart was created, whereas the other maneuver acted to improve venous return, thereby diminishing the intensity of reflex adrenergic activity.

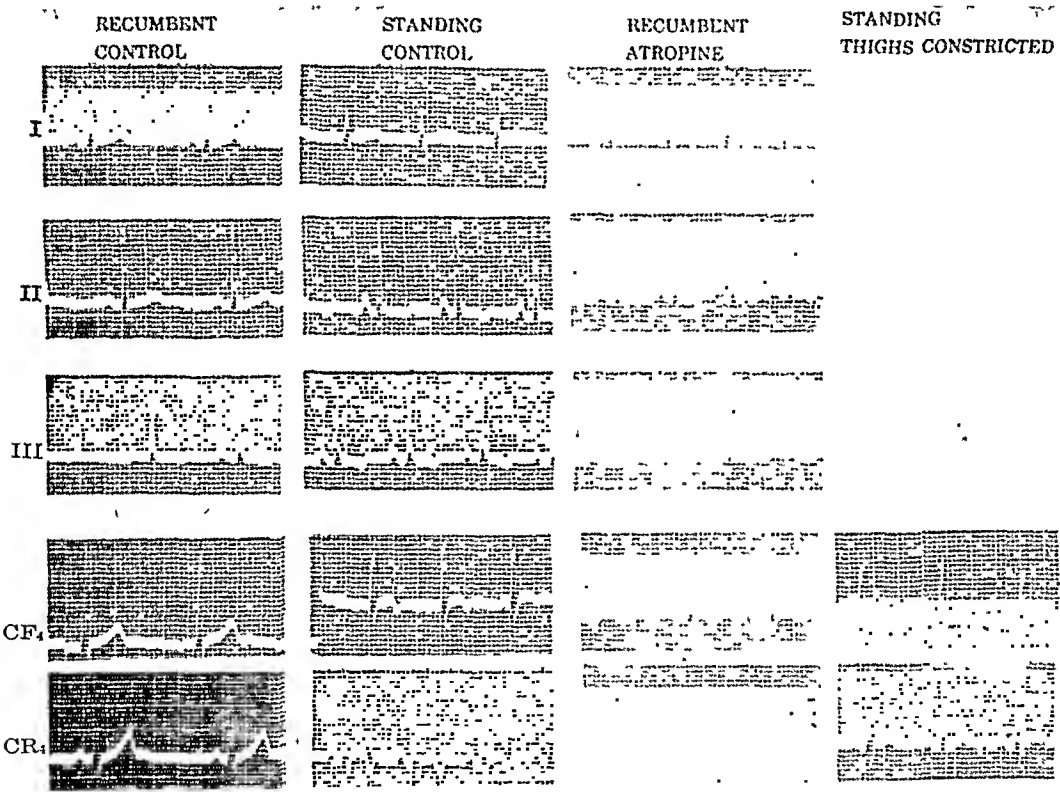


Fig. 5.—Case 4. The electrocardiogram is discussed in the text.

In this case, too, cardiac mobility must be dismissed as a cause for the original orthostatic aberrations of the ventricular deflection. Otherwise, the correction of the orthostatic distortions of the T wave by ergotamine tartrate or compression of the thighs would be difficult to explain.

CASE 4.—1. Moderately pronounced orthostatic distortions of the T waves in limb leads II and III and in precordial leads CF₄ and CR₄ developed, in association with some cardiac acceleration, although a true orthostatic tachycardia did not occur. The heart rate in recumbency was approximately 60 beats per minute and in the upright position approximately 95 beats per minute (Fig. 5).

2. In the electrocardiogram made with the subject recumbent, after the administration of a vagoparetic drug such as atropine sulfate, the T wave in all leads became con-

siderably more bizarre, but these changes in the ventricular deflection were associated with a more significant cardiac acceleration (Fig. 5).

3. In the electrocardiogram made with the subject in the upright position after compression of the thighs, the T waves in Leads CF₁ and CR₁ (which were the only leads available for inspection) reverted to a positive deflection. This change in the T wave was associated with a decrement in the heart rate of only 12 beats per minute (Fig. 5).

Comment.—Although orthostatic T-wave distortions in the limb leads developed in association with a moderate degree of cardiac acceleration, even more profound changes in the ventricular deflection were seen when the electrocardiogram was made with the subject recumbent, after the administration of atropine sulfate. Obviously, the disparity is not to be related to differences in cardiac rotation, since the ventricular deflections in the precordial leads in the orthostatic electrocardiogram were normalized merely by a maneuver (compression of the thighs), which could not possibly influence the position of the heart within the chest. It must therefore be concluded that the configuration of the T wave is related to the heart rate in one of two ways: first, that the more rapid the rate, the shorter the diastolic period and hence the more abnormal the T wave, or, second, that the increase in rate and the T-wave changes are separate chronotropic and dromotropic effects, respectively, of heightened sympathetic activity. The first interpretation does not seem to be applicable, since, in this instance, the orthostatic T-wave distortions were associated with a heart rate of less than 100 per minute, which was hardly sufficiently high to shorten the diastolic period enough to distort the T waves.

CASE 5.—1. On the day of admission, in the routine tracing obtained in the recumbent position, there was a sinus tachycardia with a heart rate of 140. The T waves were considerably distorted in Leads II and III (Fig. 6).

2. On the following day, in the recumbent position, the tachycardia had disappeared and the T waves were normal (Fig. 6).

3. Distortions of the T waves in Leads II and III, identical with those which were evident in the recumbent electrocardiogram on the day of admission, were provoked by the upright position even though the degree of cardiac acceleration was much less pronounced (Fig. 6).

4. The orthostatic distortions were prevented by a sympathetolytic drug, such as ergotamine tartrate. This prevention of the orthostatic T-wave distortions was associated with some retardation of the orthostatic cardiac acceleration (Fig. 6).

5. A vagoparetic drug such as atropine sulfate produced in the recumbent electrocardiogram distortions of the T waves in Leads II and III which are comparable to those which resulted from the upright position (Fig. 7).

6. The orthostatic T-wave distortions in Leads II and III were also abolished in large part by constriction of the thighs. This effect was also associated with a retardation of the orthostatic acceleration of the heart (Fig. 7).

7. A sympathicomimetic drug, such as amyl nitrite, produced in recumbency, some cardiac acceleration and inverted the T waves in Lead II to the same extent as did a vagoparetic drug or the assumption of the upright position (Fig. 7).

8. The Flaek maneuver, in recumbency, was followed by an inversion of the T wave in Lead II, resembling the distortion of this deflection which is produced by a sympathicomimetic drug such as amyl nitrite, by a vagoparetic drug such as atropine sulfate, or by the assumption of the upright position (Fig. 7).

Comment.—It is evident that in this case cardiac acceleration was constantly an associated feature in those electrocardiograms in which abnormal T waves appeared in Leads II and III. For this reason, the bizarre T waves would seem to be related to the tachycardia with its resultant shortening of the diastolic period. This view seems to be supported by the fact that the orthostatic distortions of the T wave are abolished when the heart rate in the upright position is reduced by a sympathetolytic drug or by compres-

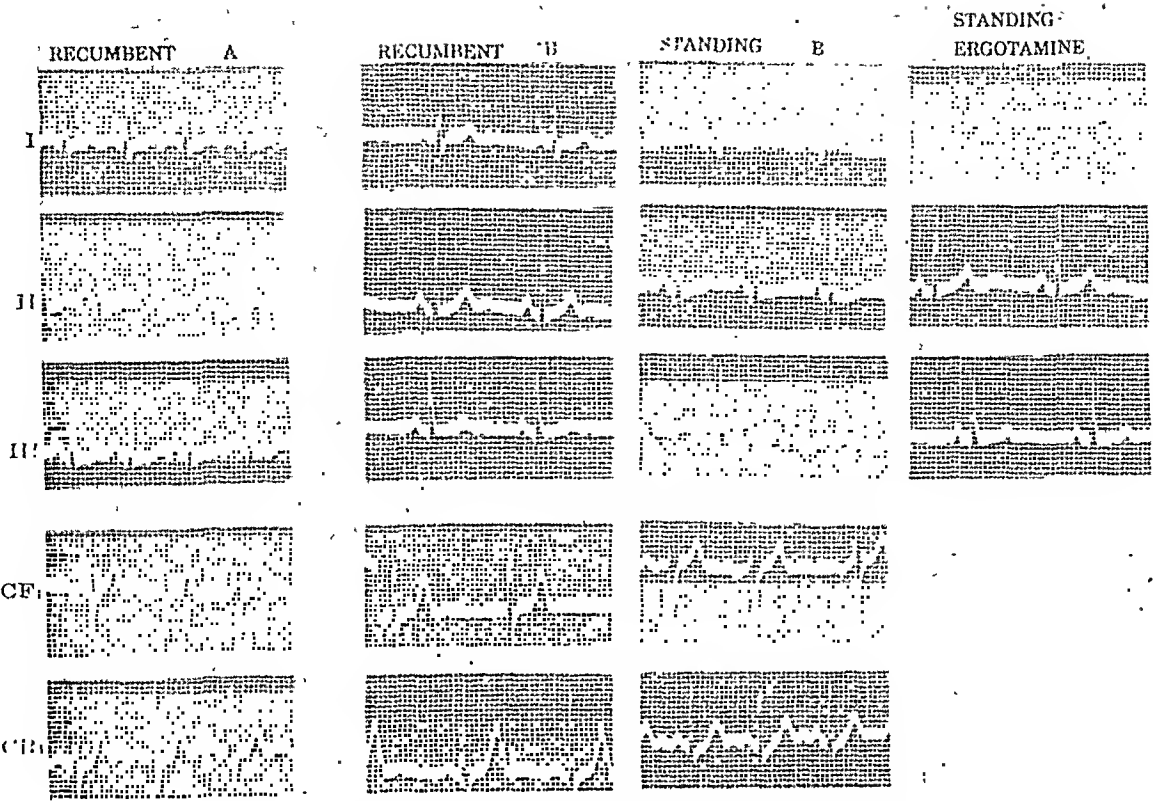


Fig. 6.—Case 5. The electrocardiogram is discussed in the text.

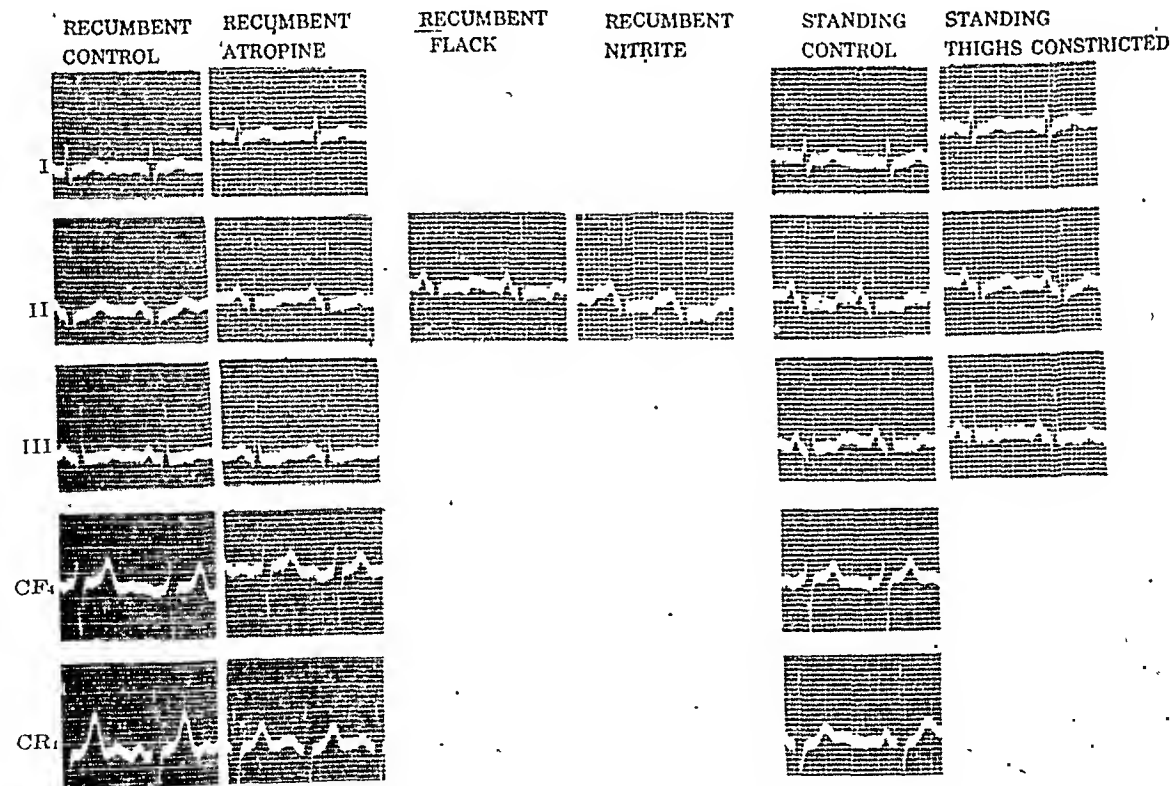


Fig. 7.—Case 5. The electrocardiogram is discussed in the text.

sion of the thighs. On the other hand, the Flack test, which is known to reflexly excite adrenergic activity by diminishing venous return,⁹ inverts the T wave without accelerating the rate (Fig. 7). This might imply that an augmented sinus rate and a concomitant T-wave distortion can be considered separate chronotropic and dromotropic effects, respectively, of heightened sympathetic activity, and that the two need not necessarily always act in combination to the same degree. In extension of this concept, the salutary effect of a sympathetolytic drug or of compression of the thighs on the orthostatic T-wave distortions would be interpreted to indicate that both of these procedures have inhibited, in a selective manner, both the chronotropic and dromotropic effects of heightened sympathetic activity provoked by the upright position.

The remarks which have been incorporated in the discussion of the previous cases, concerning the possible relationship between cardiac mobility or impaired coronary flow and the orthostatic T-wave distortions, apply also to this case.

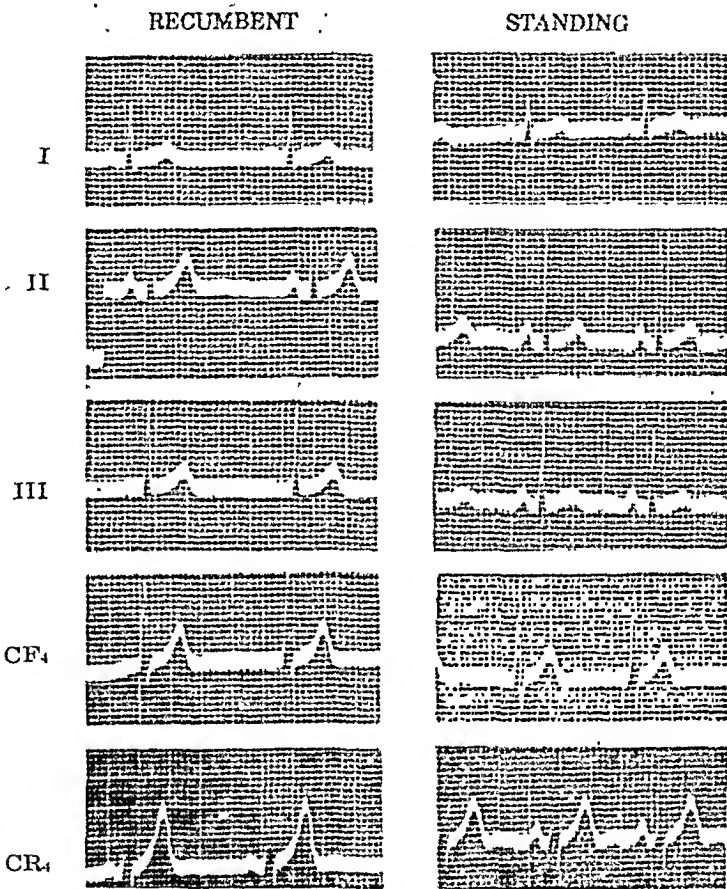


Fig. 8.—For description, see text.

DISCUSSION

Although we have presented evidence which seems to refute the interpretation that a change in cardiac rotation^{1, 2} or a diminution in coronary flow³ is chiefly responsible for the T-wave distortions which develop in Leads II and III when an electrocardiogram is made with the subject standing, it is not the intent of this report to discredit the practice of obtaining orthostatic records in cases of neurocirculatory asthenia. On the contrary, it is considered by us to be a useful procedure in the study of patients with functional cardiovascular disturbances, since such provocative aberrations of the ventricular deflection apparently offer a simple objective method for the recognition of an under-

lying vegetative disorder. Support for this view is to be found in the observations of one of us⁵ that, in emotionally stable individuals, even though they are of asthenic habitus, the assumption of the upright position will not induce significant T-wave changes (Fig. 8). Supposedly, in the normal subject, the orthostatic augmentation of sympathetic activity which physiologically develops because of the vascular readjustments which accompany the vertical stance⁹ is not in itself adequate to produce a registrable dromotropic effect upon the events associated with electrical systole, even though a chronotropic effect is evident in the moderate cardiac acceleration which occurs. Orthostatic T-wave distortions in patients with neurocirculatory asthenia are therefore presumed to represent additive sympatheticomimetic effects, i.e., reflex adrenergic activity superimposed on a state of autonomic imbalance with sympatheticotonic preponderance. The latter is believed to arise from the anxiety, with its attendant disruption of normal vagosympathetic relationships,

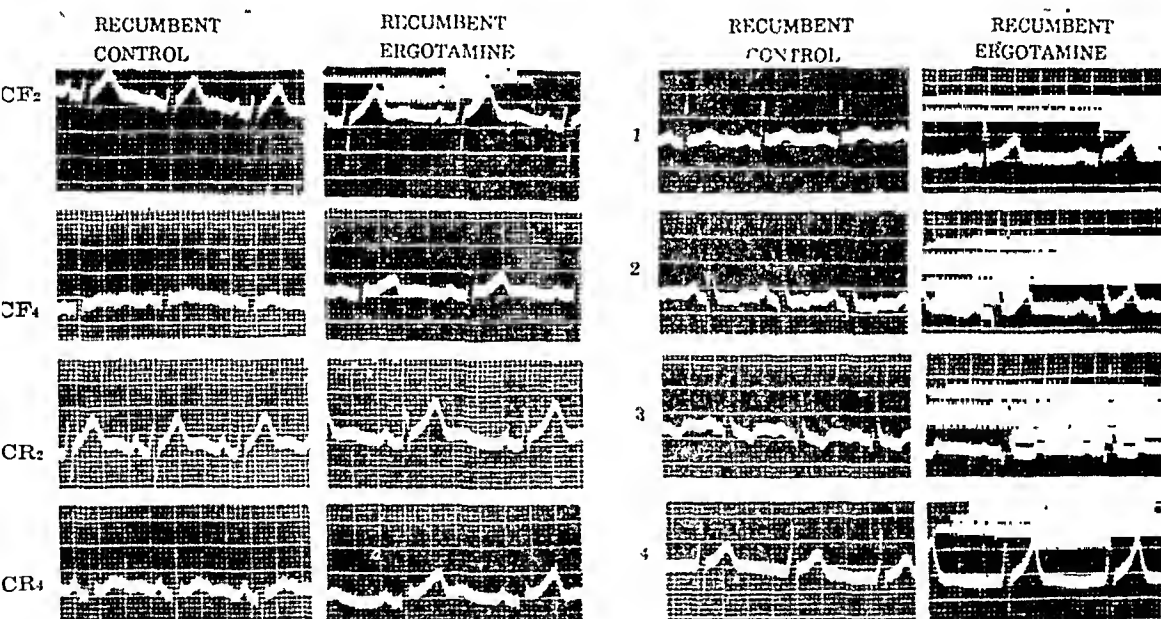


Fig. 9.—For description, see text.

which is recognized to be a fundamental component in the syndrome of functional heart disease.¹⁰ It is also conceivable that, when the dysfunction of the vegetative nervous system is sufficiently profound, the resulting sympathetic overactivity may express itself in much the same manner as it has in the precordial leads in emotionally unstable persons,¹¹ so that spontaneous T-wave aberrations will appear in Leads II and III even when the electrocardiogram is made with the subject recumbent. Actually such changes have been noted, in not a few instances, in cases of neurocirculatory asthenia^{4, 5} and, as in the case of analogous T-wave alterations in the precordial leads,¹¹ the mechanism responsible for them seems to be established from the normalization which follows the administration of a sympathetolytic drug, such as ergotamine tartrate (Fig. 9). Therefore, it would appear that this simple testing method

can be utilized to distinguish neurogenic T-wave changes from those due to intrinsic heart disease, and thus provide a means for the proper appraisal of aberrations of the ventricular deflection which occur without any other evidence of structural cardiac disease.

SUMMARY

1. It has been demonstrated, in a study of 25 patients with neurocirculatory asthenia, that heightened sympathetic activity, rather than a change in cardiac rotation or a diminution in coronary flow, is chiefly responsible for abnormalities of the T wave which appear in Leads II and III in electrocardiograms made with the subject recumbent or standing.

2. Since a fundamental component of neurocirculatory asthenia is a disruption of normal vago-sympathetic relationships, it is possible to reconcile with this disorder such "sympatheticogenic" aberrations of the ventricular deflections.

3. The body build does not seem to be the factor responsible for T-wave changes in neurocirculatory asthenia, since such abnormalities have been observed in those of sthenic and asthenic habitus.

4. The experience gained from the present study suggests that the reaction to ergotamine tartrate provides a simple means for differentiating "sympatheticogenic" distortions of the T waves from those due to intrinsic cardiac disease.

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A METHOD FOR THE ORTHODIAGRAPHIC MEASUREMENT OF THE TRANSVERSE DIAMETER OF THE HEART BY MEANS OF THE SIMPLE FLUOROSCOPE

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THE transverse diameter of the heart, measured by the orthodiagraphic method, is widely accepted as the most significant measurement upon which to base a judgment of the heart size. This report describes a method by which a true orthodiagraphic measurement of the transverse diameter may be made by means of the ordinary fluoroscope without the standard orthodiagraphic equipment. The principle of the method is simple. If a vertical line, drawn at the center of the screen, is aligned first with one border of the heart shadow and then with the other border, by moving the screen laterally, then the distance through which the screen is moved is equal to the transverse diameter. This is a necessary consequence of the fact that the screen and the tube are rigidly connected and move as a unit. The amount of this lateral movement might be measured by a tape reaching from the screen to a near-by wall or by a plumb-line reaching from the screen down to a scale on a table below the screen. Neither of these methods would be quite convenient in actual practice, but the method now to be described accomplishes the same purpose expeditiously and accurately with the simplest accessories. The actual technique first will be described and then, by means of diagrams, the logic of the procedure will be set forth.

The accessories required are the following:

1. A wood tongue depressor on which are mounted, by means of adhesive plaster, two triangular pieces of lead placed with their vertical sides parallel and exactly 10 cm. apart, with the apices that are opposite the vertical edges pointing toward each other (Fig. 1). The line, 10 cm. long, between the vertical edges will be called the "base line."
2. A thin, straight wood stick, such as an ordinary wood applicator.
3. A grease pencil.
4. A centimeter scale.

PROCEDURE

The patient is placed in the usual position for fluoroscopy and the tongue depressor, with the lead triangles, is attached by adhesive plaster to the anterior chest wall, horizontally and centrally, at about the level of the second costal cartilages. It is necessary that the lead triangles be equidistant from the screen; therefore, if the chest is irregularly shaped, it may be necessary

to bring forward one end of the tongue depressor by means of a wad of paper or cotton. The screen is set vertically close to the body of the patient but not in contact with it. The screen must be free to move laterally, but its distance from the patient must not vary during the observation. The stick is then attached vertically at the center of the screen by a bit of adhesive plaster. If the fluoroscope is used frequently for heart studies it is convenient to have a vertical black line painted on the screen, in place of the stick.

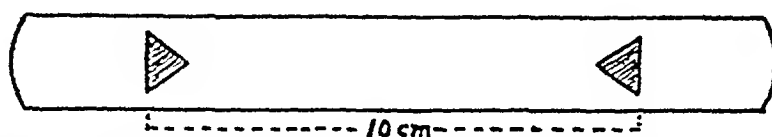


Fig. 1.—Wood tongue depressor with lead triangles attached. The interval between the vertical edges of the triangles measures 10 cm. and is called the "base line."

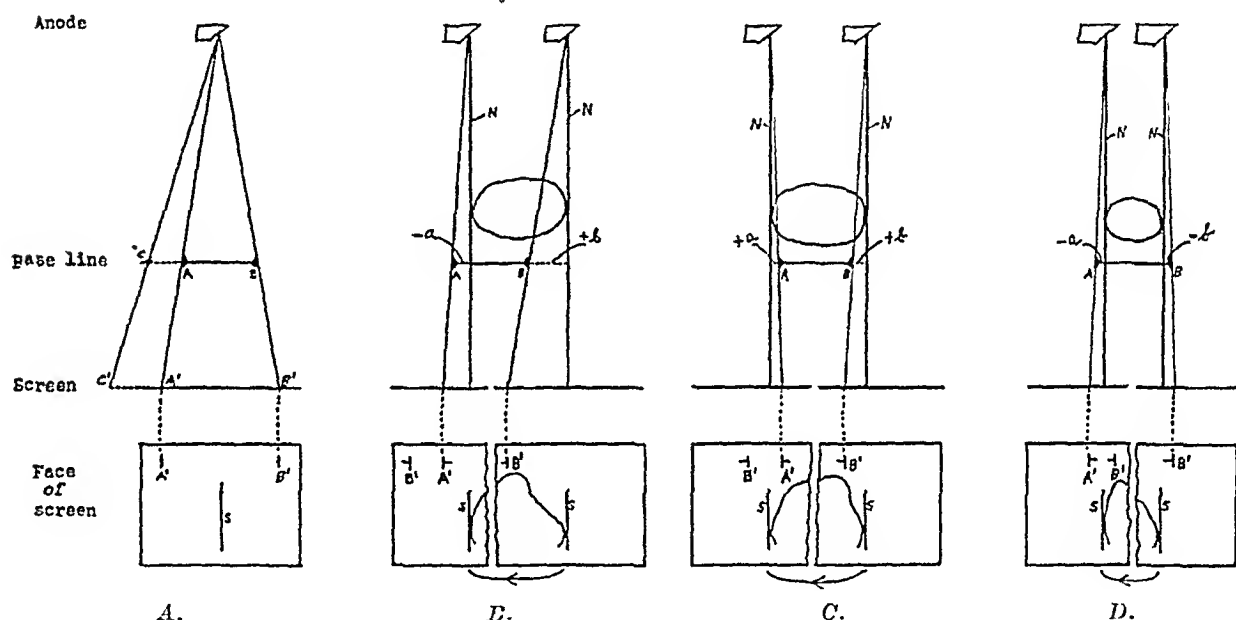


Fig. 2.—Diagrams illustrating the geometric principle on which is based a new method of measuring the transverse diameter of the heart. The upper portion of each diagram represents the relation of the target, heart, base line, and screen, shown in horizontal plan; the lower portion of the diagrams represent the face of the screen, seen in vertical elevation. Letters have significance as follows: *A* and *B*, left- and right-hand lead triangles, 10 cm. apart; the interval, *AB*, is called the "base line." *A'* and *B'*, marks on screen indicating positions of shadows of lead triangles. *a* and *b*, end corrections to be added to or subtracted from length of base line. *N*, the line of intersection of the "normal plane" and the plane of the diagram. *S*, the stick attached at the center of the screen. Diagram *A*, The magnification ratio is given by $A'B'$ divided by AB . When this ratio is known any interval on the base line, AB , or on an extension, such as AC , may be calculated readily from the measured length of the similar interval, $A'C'$, on the screen. Diagrams *B*, *C*, and *D* represent different positions and sizes of heart. In each diagram two successive positions of the screen and target are represented. The position to the right precedes that to the left. *B'* is marked when the screen is in the first position. After the screen is moved to the left *A'* is added. The interval, $A'B'$, corrected for magnification, is added to, or subtracted from, the length of the base line, AB , to give the transverse diameter of the heart.

When the screen is illuminated the shadows of the lead triangles will appear, lying somewhat above the shadow of the heart and separated by a distance of somewhat more than 10 centimeters. The stick will appear in the midst of the heart shadow but rather nearer to the right border if the patient and the screen have been centered in the usual manner. Unless the screen has an exceptionally long range of lateral motion it now will be necessary, in

most cases, to have the patient move a little to his right until the stick appears to lie at about the center of the transverse diameter of the heart shadow. Thereafter the patient should remain immobile.

The remainder of the procedure will be described as comprising four steps.

Step 1.—(Fig. 2, *A*.) The upper angles of the shadows (*A'* and *B'*) of the lead triangles are marked on the screen with the grease pencil. The distance in centimeters between these marks, to be measured after the whole observation has been completed, divided by 10, gives the "magnification ratio," a number that is to be used as a correction to later measurements.

Step 2.—(Fig. 2, *B*.) The screen, with the tube, is moved to the observer's right until the stick appears tangent to the left border of the heart shadow. Then the lower angle of the shadow (*B'*) of the right-hand* triangle (*B*) is marked on the screen, using a short vertical line drawn downward from the angle and a short horizontal line indicating the direction of the apex of the triangle. The mark then will appear as a letter T placed on its side; thus, —|.

Step 3.—(Fig. 2, *B*.) The screen is moved to the observer's left until the stick appears tangent to the right border of the heart shadow. The lower angle of the shadow (*A'*) of the left-hand triangle (*A*) is marked on the screen, using the same symbol as that for Step 2, but reversed; thus |—.

Step 4.—(Fig. 2, *B*.) The interval between the two marks (—| and |—) now is measured. This measurement is divided by the magnification ratio and the quotient is added to 10 centimeters. The sum is equal to the transverse diameter of the heart.

DISCUSSION

A vertical plane passed through the target and the stick is approximately perpendicular to the screen. The plane, when placed tangent to one heart border, is parallel to its position when placed tangent to the other border. If the plane is nearly perpendicular to the screen the distance between its two positions, when placed tangent to the two heart borders in succession, is equal to the true radiologic "transverse diameter" of the heart. In what follows, the plane will be called the "normal plane," whether placed at the right border of the heart or at the left border.

The base line defined by the two lead triangles on the anterior surface of the chest is a device for measuring the interval between the two positions of the normal plane when the latter is placed in succession at the left and the right border of the heart. The method may be compared to the measurement of an object, for example the top of a desk, by means of an ungraduated, 5-foot pole together with a graduated foot rule. Neither end of the pole need be aligned exactly with the edge of the desk top; the extent to which it extends beyond or falls short can be measured by the foot rule and the intervals added to or subtracted from 5 feet. The diagrams in Fig. 2 show the application of this principle to the fluoroscopic problem. The base line on the chest remains fixed

*The words "right" and "left" are used to signify direction relative to the observer, except where the reference is to a border of the heart; in the latter case the words are used with the usual anatomic significance.

and the intervals (a and b) between its ends and the normal plane are determined first at the left border of the heart and then at the right border. The magnitudes of these intervals are calculated from the measured corresponding intervals on the screen reduced by division by the previously determined magnification ratio. When the normal plane is placed at the left border of the heart if the right hand shadow lies to the left of the stick then the right end of the base line falls short of the normal plane and the corrected measured interval on the screen is to be added to the length of the base line, whereas if the shadow lies to the right of the stick the right end of the base line reaches beyond the normal plane and the corrected measured interval is to be subtracted from the length of the base line. The same procedure is carried out at the right border of the heart, the left-hand shadow and the left end of the base line being considered. The several possible relations are illustrated in Fig. 2. In B , TD (transverse diameter) $= 10 \text{ cm.} + b - a$; in C , $TD = 10 \text{ cm.} + b + a$; in D , $TD = 10 \text{ cm.} - b - a$. For an understanding of the method it is necessary to see how these end corrections may be calculated and applied, as in these examples, but, fortunately, in practice the two end corrections do not need to be considered separately, for the geometric relations are such that the interval between the two marks, A' and B' , on the screen, when divided by the magnification ratio, is equal to the algebraic sum of the two end corrections. Hence the simple procedure of Step 4 as described previously, is valid and the observer is spared some time and effort. If the TD of the heart is less than 10 cm. this combined correction always is negative, but it is always positive if the TD is greater than 10 centimeters. In the case of a small heart, with a TD near 10 cm., the observer might be in some doubt about the sign of the small correction, but in this case another characteristic of the geometric relations provides the answer; it may be seen from the figures that when the marks "face" each other ($—| |—$) the correction always is positive; when they are turned away from each other ($|— —|$) the correction always is negative.

The geometric principle on which this technique is based is simple and obvious, so that an a priori conviction of the soundness of the method reasonably may be entertained. However, the results given by the method have been compared with measurements obtained in the same cases by the use of standard orthodiagraphic equipment. The discrepancies in the results, a few millimeters at the most, can be explained fully by some uncertainty about the exact location of the border of the heart's shadow. Obviously this uncertainty affects the standard orthodiagraphic method as much as it does the method here described.

In practice, this new method has been found simple and expeditious. Although the explanation of the procedure may give the impression of complexity, the fact is that after a few repetitions the steps seem obvious and are easily remembered. Equipped with this method a clinician who has only a simple fluoroscope is enabled to measure the most significant dimension of the heart with satisfactory accuracy and can thus estimate the heart's size and follow the changes in size during treatment.

THE EFFECT OF SPLANCHNIC RESECTION ON THE PERIPHERAL BLOOD FLOW AND RECTAL AND SKIN TEMPERATURES IN HYPERTENSION

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IN A PRECEDING paper we have described observations relating to the peripheral blood flow and skin and rectal temperatures in patients with essential hypertension.¹ In those studies we found that the peripheral blood flow was decreased in persons with essential hypertension as compared with normal young subjects, that the rectal temperature was higher in hypertension, but the average weighted skin temperature was lower in subjects with hypertension than in normal subjects. Moreover, roughly speaking, the upper part of the body was warmer and the lower part colder in hypertension than in normal subjects indicating a greater blood flow in the upper part of the body and a lesser peripheral blood flow in the lower part of the body in hypertensive patients. There are, then, fundamental differences in the distribution of blood to the periphery in hypertensive patients as compared with normal subjects, and as compared with patients exhibiting hypertension as a part of coarctation of the aorta² and pheochromocytoma.³

The medical treatment of hypertension has neither yielded results which were uniformly successful nor has it significantly altered the natural history of the disease (Stewart⁴ and Atchley⁵). As a consequence there have come in rapid succession in recent years the attempts to lower blood pressure in arterial hypertension by surgical procedures designed to interrupt sympathetic nerve pathways. At first partial sympathectomy was done (Craig and Brown⁶ and Craig⁷). Then anterior nerve root section was carried out (Adson and Brown,⁸ Adson,⁹ Heuer,¹⁰ and Page and Heuer^{11, 12}). Then followed in succession the attempts to interrupt the sympathetic nerves more completely (Allen and Adson,¹³ Smithwick,^{14, 15} Peet, Woods, and Braden,¹⁶ Peet and Woods,¹⁷ and Grimson^{18, 19}). Since then additional reports have been made by other observers.²⁰⁻²⁴ A fall in blood pressure is achieved by these surgical measures in a certain number of subjects. It appears that the so-called Smithwick procedure^{14, 15} is one of the most effective.

Since the peripheral blood flow in hypertensive patients shows certain differences from normal individuals we wished to see how the peripheral blood flow and rectal and skin temperatures were altered in these same hypertensive

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patients when the splanchnic nerves were sectioned with the objective of lowering the blood pressure. Such observations form the subject of this paper. In the earlier part of these studies the sub- and supradiaphragmatic resection of the greater, lesser, and least splanchnic nerves on both sides was done in succession at ten-day to two-week intervals.^{*} In the later operations, done after 1940, the Smithwick operation was carried out.^{14, 15} In this operation there is bilateral removal of the entire great splanchnic nerve with division of all of its aortic branches coupled with interruption of the communicating rami of the ninth to the twelfth dorsal segments, inclusive, and the first and second lumbar ganglia, together with excision of the sympathetic trunk over this area. The two sides are operated upon at ten-day to two-week intervals. The splanchnic bed is the mechanism of the human organism for maintaining the level of blood pressure essentially constant in changing from sitting to lying and standing position, and removal of the sympathetic impulses affecting the caliber of this bed has been found to give, in certain instances, a reduction of elevated blood pressure to normal levels, regression of retinal changes, and a disappearance of symptoms which were associated with hypertension.

Since 1939, observations have been made on 7 patients before and after the less complete operation of splanchnic resection, and on 19 patients before and after the Smithwick operation. The surgical aspects of these studies will be reported elsewhere.²¹

METHODS

The peripheral blood flow was measured by our modification^{25, 26} of the method of Hardy and Soderstrom.²⁷ The methods used were described in the earlier paper¹ and need not be repeated. Peripheral blood flow was expressed as cubic centimeters per square meter per minute. In the course of the observations records were made of rectal temperature and of the temperatures of eleven areas on the anterior surface of the body (Fig. 1) from which the average weighted skin temperature could be estimated, of basal metabolic rate, of blood pressure, and of heart rate.

Plan of Procedure.—The plan of making the measurements of peripheral blood flow was described in a preceding paper.¹ All measurements were made with the patients in a basal metabolic state. The peripheral blood flow was measured on one or more occasions to secure control or preoperative levels of peripheral blood flow and of the other data. Shortly afterward the splanchnic nerves were sectioned on one side. When the patient had recovered from this procedure ten to fourteen days later, the observations relating to peripheral blood flow were repeated, after which the splanchnic nerves on the other side were sectioned. Ten days to two weeks later still, the observations relating to peripheral blood flow were repeated as well as at longer intervals after the completed operation. When patients returned for observations after discharge from the hospital, they were hospitalized overnight in order to be kept in a basal state

^{*}The earlier operations were done by Dr. Frank Glenn and the later ones by Dr. Bronson Ray. We wish to thank these members of the Department of Surgery for their cooperation in making these studies possible.

for the observations the next morning. Occasionally, if patients lived near by, they came to the hospital by taxi early in the morning before breakfast and rested sufficiently long to insure basal conditions. All observations were made at

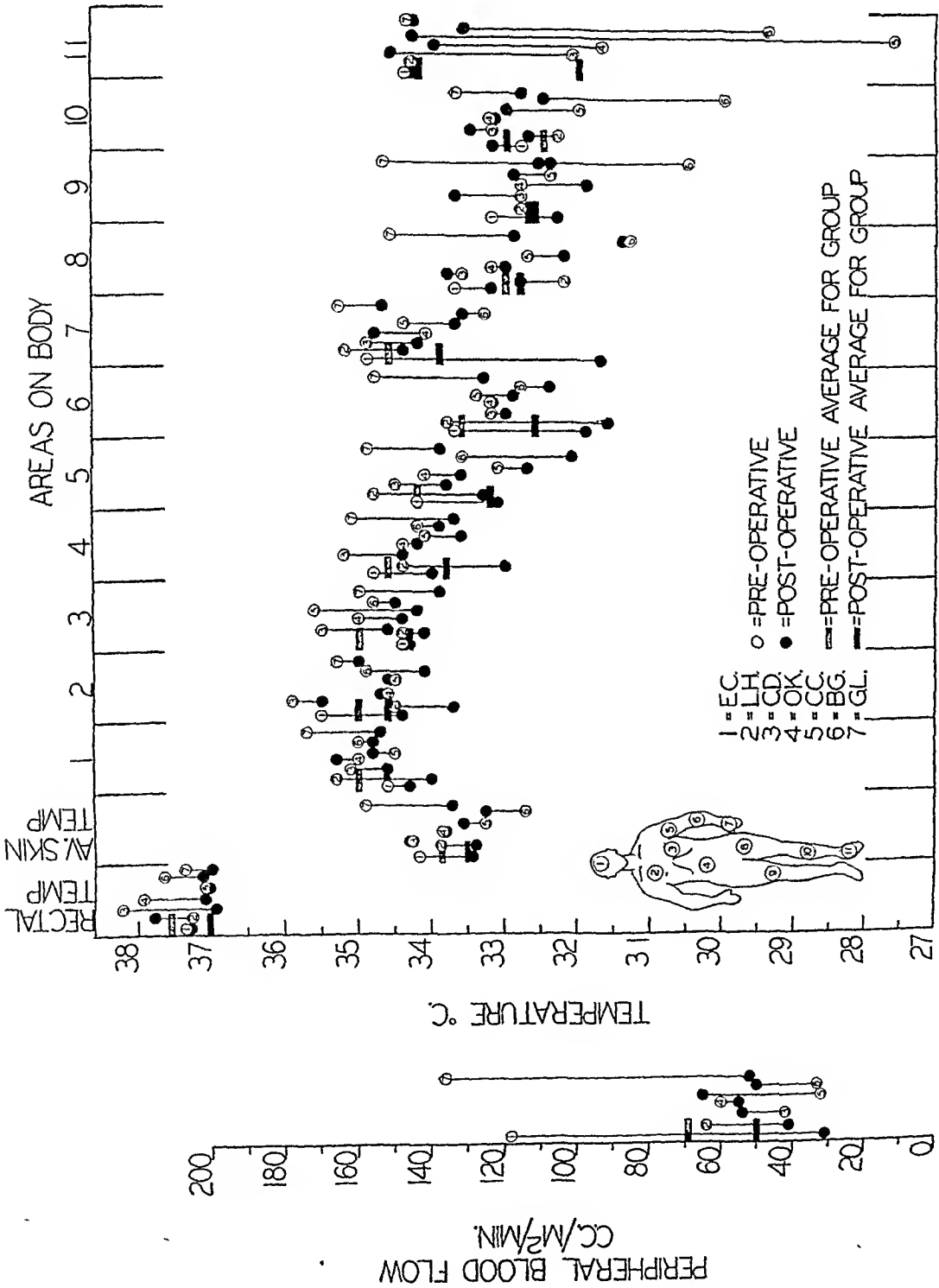


Fig. 1.—In this figure are shown data, relating to patients with hypertension who had the Smithwick operation, and in whom the blood pressure fell to normal after operation (Table I). The numbers in the open circles in the chart refer to the patients indicated. The open circles refer to measurements made before operation, and the closed circles refer to the measurements made when the blood pressure was normal after operation. The solid and stippled bars indicate the averages of all the patients.

a room temperature of 27° C. with a humidity of 45 to 50 per cent. The peripheral blood flow and temperatures and other data recorded in Table I represent the averages of all the observations made for that morning.

Those having the partial operation are separated in Table I from those in whom the Smithwick procedure was done. Moreover, since the object of the surgical procedure was to lower the blood pressure, the patients were grouped into those in whom the blood pressure fell to normal after operation, those in whom the blood pressure fell moderately, and those in whom the blood pressure was unaffected by operation. This was done in order to ascertain whether any changes in the peripheral blood flow and skin and rectal temperatures were brought about in these respective groups as a result of the surgical procedure.

OBSERVATIONS

Observations Relating to Those Patients Subjected to the Smithwick Procedure in Whom the Blood Pressure Fell to Normal Limits.—In seven patients, six women and one man, the blood pressure fell to normal following the Smithwick operation. In them we have compared the preoperative measurements of the circulation with those made when the blood pressure after operation was at normal levels. The average of the blood pressure for the group was 178/120 before and 124/89 after operation. The average rectal temperature, which was 37.54° C. before operation, that is to say higher than normal²⁸ (Table I, Fig. 1), fell to 37.01° C., but still remained higher than normal. The average weighted skin temperature which was 33.86° C. before operation fell to 33.49° C., that is to say below normal. While these were the trends with respect to rectal and average weighted skin temperatures, statistical analysis showed that they were probably not significant changes. The temperature for areas of the upper part of the body fell as compared with the preoperative levels. These areas were: Areas 1 to 6 and included the forehead (Area 1), the upper chest (Area 2), the lower chest (Area 3), the abdomen (Area 4), the upper arm (Area 5), and the forearm (Area 6). The temperatures of the upper (Area 8) and lower thigh (Area 9) were essentially unchanged by the operation but the temperature of the leg (Area 10) and of the foot (Area 11) *increased* very much; the rise in temperature in the latter was 2.2° C. The greatest fall in temperature after operation, namely 1° C., was in the upper arm (Area 5) and forearm (Area 6). The changes in temperature in these areas were consistently in this direction. The greatest rise in temperature, namely 2.2° C., occurred in the foot (Area 11); on statistical analysis this is slightly significant. There was fall in the average peripheral blood flow from 69 c.e. per square meter per minute to 50 c.e. per square meter per minute. The blood flow, however, varies considerably in individual patients; in some patients the peripheral blood flow increased after operation, while in others it decreased. The change is not significant. The basal metabolic rate before operation averaged +3 per cent and after operation, -7 per cent.

Observations Relating to Those Patients Subjected to the Smithwick Procedure in Whom Blood Pressure Decreased Moderately but Did Not Reach Normal.—Seven patients, three men and four women, were in this group (Table I, Fig. 2). The average of the blood pressures before operation was 213/125 and after operation it was 182/112. After operation the rectal temperature was essentially unchanged. The average skin temperature for all the individual

TABLE I. OBSERVATIONS RELATING TO THE PERIPHERAL BLOOD FLOW, AND SKIN AND RECTAL TEMPERATURES IN HYPERTENSIVE PATIENTS BEFORE AND AFTER SPLENECTOMY UNDERTAKEN TO LOWER THE BLOOD PRESSURE

NAME HIST. NO. SEX AGE (YRS.)	DATE	PERIPH- ERAL BLOOD FLOW C.C./M ² / MIN.	RECTAL TEMPER- ATURE ° C.	AVERAGE WEIGHTED SKIN- TEMPER- ATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG.	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS	TIME RELATION TO OPERATION
					TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE															
					1	2	3	4	5	6	7	8	9	10	11					
Smithwick Operation Followed by Decrease in Blood Pressure to Normal																				
E. C. 380212 F. 46	3/24/44* 4/17/44 5/ 5/44 6/ 9/44†	118 26 39 31	37.34 37.27 36.89 37.11	34.17 33.35 33.41 33.44	34.6 34.6 34.2 34.3	35.5 35.0 34.3 34.4	34.4 33.9 33.9 34.0	34.8 33.4 33.0 33.1	33.7 33.3 32.8 31.9	34.9 34.5 34.5 31.7	33.7 32.3 32.2 33.2	33.2 32.0 31.7 32.3	32.8 31.4 33.3 33.2	32.3 32.0 32.3 32.3	34.3 33.5 34.3 34.3	182/116 192/109 178/110 137/ 96	+12 - 3 - 5 - 4	Essential hyperten- sion. Enlarged heart	Preop. 13 d. after R. R/L 40/24† Postop. 2 mo.	
L. H. 351566 F. 44	2/ 1/44* 2/12/44 2/14/44 3/ 4/44 3/10/44 6/10/44†	64 95 63 27 42 41	37.25 37.54 37.38 37.17 36.73 36.76	33.87 34.20 33.90 33.57 33.17 33.39	35.3 34.8 34.9 35.0 34.4 34.0	34.5 35.1 34.2 34.3 34.1 33.7	34.4 33.6 33.9 33.4 33.3 33.0	34.8 34.5 35.1 33.6 32.5 33.3	33.8 33.9 35.3 33.4 32.3 31.6	35.2 35.8 35.3 35.0 34.1 34.4	32.2 33.0 32.3 31.9 31.6 32.8	32.2 32.8 32.3 32.6 32.0 32.7	32.3 33.4 32.4 32.4 32.0 32.7	34.3 35.6 35.1 33.6 34.1 34.3	166/111 166/110 164/110 113/ 74 111/ 78 106/ 71	+ 2 + 8 + 0 -20 - 7 -10	Hypertension. En- larged heart	Preop. 10 d. after L. 12 d. after L. L/R 31/18 L/R 37/24 Postop. 4 mo.		
C. D. 372511 F. 25	12/ 7/43* 1/18/44 1/21/44 2/ 4/44 2/23/44† 5/19/44	42 103 95 104 54 37	38.20 37.24 37.26 37.16 36.93 36.55	34.25 34.70 34.75 34.96 34.27 33.50	35.1 35.0 35.2 35.7 34.6 34.2	35.9 35.8 35.8 35.3 35.5 35.3	35.5 35.3 35.6 35.4 34.6 34.7	34.5 33.9 34.4 34.6 33.8 33.2	33.2 33.2 33.7 34.3 34.5 31.4	34.9 35.2 35.4 35.4 34.2 28.7	33.6 32.8 33.7 34.4 34.3 33.6	32.8 34.4 34.3 32.9 33.5 32.9	33.2 34.2 34.6 33.7 33.5 33.0	32.9 34.7 34.3 32.6 34.6 34.7	184/137 140/107 154/116 138/103 136/ 98 162/116	- 6 - 8 -16 - 9 -24 -14	Hypertension. Rheu- matic heart dis- ease. Mitral in- sufficiency and stenosis. En- larged heart	Preop. L/R 30/27 L/R 42/30 L/R 56/44 L/R 2 mo. 13 d./2 mo. 1 d. Postop. 5 mo.		
O. K. 368408 F. 38	1/12/44* 1/25/44 2/ 8/44 2/11/44 2/28/44† 6/29/44	60 78 36 52 55 65	37.92 37.40 37.84 37.73 37.08 36.89	33.85 34.13 33.59 33.88 33.84 33.68	35.0 35.4 35.1 35.0 35.3 34.2	34.6 35.1 34.4 34.6 34.7 34.2	35.0 34.8 35.1 35.2 34.4 34.6	34.4 34.9 34.3 34.7 34.2 34.0	33.2 33.7 34.0 32.6 32.8 32.0	34.1 35.3 34.7 34.7 34.8 32.0	33.2 32.6 31.8 32.8 33.0 32.7	32.8 33.3 31.4 31.4 31.9 32.6	32.8 34.0 32.4 33.1 33.2 33.8	31.7 34.0 34.5 34.5 34.0 34.4	209/132 199/121 151/105 148/109 125/ 95 135/ 90	78 78 112 108 88 70	- 5 - 1 - 0 + 2 -11 - 9	Essential hyperten- sion	Preop. 12 d. after R. R/L 26/11 R/L 20/14 R/L 46/31 Postop. 5 mo.	
C. C. 311597 F. 44	1/ 5/42* 1/21/42 2/14/42†	32 55 65	37.08 37.42 37.07	33.26 33.22 33.56	34.5 35.1 34.8	34.5 34.9 34.2	35.6 34.8 34.2	34.1 34.8 32.7	33.1 33.8 32.9	34.4 34.8 33.7	32.7 32.0 32.2	32.4 32.9 32.9	32.0 30.7 33.0	27.6 27.9 34.3	169/117 175/125 132/103	79 87 96	- 4 +10 - 1	Essential hyperten- sion	Preop. 14 d. after R. R/L 22/17	
B. G. 311888 F. 25	11/10/41* 1/14/42 4/ 9/42†	33 73 50	37.64 37.19 37.11	32.71 33.63 33.25	35.0 34.9 34.8	34.9 34.5 34.1	34.8 34.4 34.5	34.2 34.3 33.9	33.6 32.8 32.1	32.8 32.9 32.4	33.3 34.2 33.6	31.3 32.7 31.4	30.5 32.9 32.5	30.0 32.8 32.5	29.4 33.6 33.6	177/116 156/109 126/ 88	92 90 78	+14 + 5 - 2	Essential hyperten- sion. Enlarged heart	Preop. 27 d. after R. R/L 5 mo./ 4 mo.
G. L. 351331 M. 31 32	3/16/43* 3/22/43 4/15/43 6/20/44†	136 108 42 52	37.36 37.13 37.41 36.99	34.89 34.51 33.96 33.71	35.6 35.4 35.3 34.7	35.3 35.0 35.1 35.0	35.0 34.7 35.1 33.9	35.1 34.5 34.2 33.7	34.9 34.5 34.2 33.3	34.8 34.4 33.7 33.3	35.3 35.1 34.1 34.7	34.6 34.0 34.1 32.9	34.7 34.4 32.6 32.5	33.7 33.2 32.3 32.8	34.4 34.4 31.5 34.3	156/108 163/113 170/115 106/ 70	68 67 78 72	+ 6 + 3 +10 + 3	Essential hyperten- sion	Preop. Preop. 19 d. after L. L/R 15 mo./ 10 mo.

Average preoperative*	69	37.54	33.86	35.0	35.0	35.0	34.6	34.2	33.6	34.6	33.0	32.7	32.5	32.0	178/120	76	+ 3
Average postoperative†	50	37.01	33.49	34.6	34.6	34.3	33.8	33.2	32.6	33.9	32.8	32.6	33.0	34.2	124/ 89	78	- 7
Standard deviations about the means preoperative	39	0.37	0.62	0.4	0.5	0.4	0.5	0.6	0.6	0.7	1.0	1.2	1.1	2.6	16/ 10	7	
Standard deviations about the means postoperative	10	0.11	0.35	0.4	0.6	0.2	0.4	0.6	0.6	1.0	0.7	0.5	0.3	0.3	11/ 8	9	

Smithwick Operation Followed by Moderate Decrease in Blood Pressure

R. L. 376201 M. 19	2/10/44* 2/21/44 2/25/44 3/11/44 3/14/44 3/25/44 5/31/44†	81 99 115 68 70 59 72	36.81 37.08 37.03 36.87 36.87 36.79 36.88	33.97 34.24 34.44 34.16 34.20 33.94 34.03	34.7 34.1 35.1 34.7 34.1 34.4 34.6	34.7 34.9 35.3 35.1 34.7 34.7 34.5	34.4 34.6 34.8 34.9 34.9 34.4 34.2	34.6 35.2 35.3 34.9 35.3 34.9 34.4	33.9 34.2 34.2 33.9 34.0 33.3 33.6	33.6 33.7 34.0 33.9 34.2 33.3 33.6	35.1 34.8 35.3 35.3 34.2 34.4 35.1	33.9 34.4 34.0 33.7 33.1 33.8 33.7	33.3 33.0 33.4 33.1 33.2 33.3 33.2	32.5 33.3 33.2 32.8 32.9 33.4 33.4	212/136 168/123 210/144 203/147 216/145 193/132 192/127	82 93 99 94 88 86 81	- 5 + 1 - 10 - 10 - 15 - 15 - 5	Hypertension. Chronic Glomeru- lonephritis. Enlarged heart	Preop. 11 d. after L. 15 d. after L. L/R 30/14 L/R 32/16 L/R 44/28 Postop. 3 mo.	
S. McD. 95209 M. 48	12/ 3/43* 12/21/43 1/ 4/44 3/29/44†	25 47 55 64	37.11 37.93 37.05 36.94	33.52 33.53 33.72 33.85	34.9 35.2 35.1 34.7	34.5 34.2 34.6 34.3	33.7 33.8 34.0 33.4	33.5 34.1 34.3 33.4	33.9 34.0 34.0 34.0	33.6 33.9 34.3 34.5	34.2 34.6 34.8 34.9	33.1 32.5 33.2 32.9	32.2 32.1 33.3 33.7	33.0 32.5 31.8 33.4	32.5 33.3 32.5 34.3	177/113 156/110 162/108 157/107	68 90 74 73	- 11 - 3 - 6 - 8	Hypertension. En- larged heart	Preop. 10 d. after L. L/R 24/12 L/R 3 mo. 18 d.; 3 mo. 6 d.
W. C. 375325 M. 48	1/ 5/44* 1/ 7/44 2/ 2/44 2/ 3/44 2/19/44 2/26/44†	62 70 39 32 59 44	37.27 37.10 37.11 37.02 36.97 37.08	34.30 33.97 33.19 33.73 33.76 34.16	35.3 35.0 35.1 34.9 34.2 34.5	34.5 34.8 34.3 34.9 34.2 34.8	34.7 34.3 34.2 34.7 34.5 34.7	34.4 33.8 33.7 33.7 34.5 33.7	34.2 34.4 32.4 33.4 33.0 33.5	34.2 34.8 32.4 33.4 33.0 33.5	35.0 34.8 32.7 34.1 33.7 34.6	33.7 32.9 33.1 33.2 33.0 33.2	33.5 33.2 32.9 31.7 32.1 32.8 33.7	33.2 34.4 34.5 30.2 32.1 34.9 35.3	198/113 193/112 227/120 216/123 188/104 180/105	66 66 80 80 90 85	- 1 - 2 + 7 + 4 + 4 - 3	Hypertension. Slight enlarge- ment of heart. Myocardial infarc- tion due to arteri- osclerotic coro- nary thrombosis	Preop. Preop. 15 d. after R. 16 d. after R. R/L 32/15 R/L 39/22	
M. J. 315435 F. 43	1/ 3/44* 3/ 7/44†	82 80	37.53 37.13	34.51 33.95	35.1 34.6	35.1 33.9	35.1 34.6	35.2 34.5	34.6 33.8	34.2 33.4	35.2 34.7	34.1 33.3	33.7 32.9	33.6 33.6	241/126 191/113	65 86	- 2 - 1	Hypertension. Hy- pertensive enceph- alopathy. En- larged heart	Preop. L/R 53/40	
A. A. 318945 F. 41	2/27/42* 3/12/42 4/ 3/42†	39 32 12	37.35 37.32 37.22	33.54 33.18 33.37	34.4 34.8 34.3	34.8 34.2 34.2	34.5 34.2 34.7	34.7 33.7 33.8	32.8 32.4 32.7	33.7 33.7 33.0	34.8 34.9 34.8	33.5 32.5 32.4	32.1 31.2 31.2	31.6 31.8 32.5	32.0 208/116 211/119 181/116	73 75 75	- 10 - 10 - 21	Hypertension. Bron- chial asthma. Enlarged heart	Preop. 9 d. after R. R/L 22/13	
I. H. 287756 F. 26	4/11/44* 5/10/44†	33 77	37.47 37.37	32.01 33.88	32.2 34.8	32.7 34.3	32.3 34.6	32.4 34.1	32.4 34.4	32.4 33.6	32.9 34.9	31.6 32.1 32.9	31.2 31.2 32.9	31.2 33.7	221/148 182/118	85 68	+ 30 + 10	Hypertension	Preop. L/R 28/13	

*Preoperative measurements which were used to obtain these averages or means.

†Postoperative measurements which were used to obtain these averages or means corresponding to the lowest blood pressure after operation.
‡R/L 40/21 = 40 days after operation on right side and 21 days after operation on left side.

TABLE I—CONT'D

NAME HIST. NO. SEX AGE (YRS.)	DATE	PERIPH- ERAL BLOOD FLOW C.C./M ² / MIN.	RECTAL TEMPER- ATURE ° C.	AVERAGE WEIGHT- ED SKIN TEMPER- ATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS	TIME RELATION TO OPERATION
					° C.															
					1	2	3	4	5	6	7	8	9	10	11					
					° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.					
Smithwick Operation Followed by Moderate Decrease in Blood Pressure—Cont'd																				
V. K.	4/ 5/44*	25	36.94	32.25	34.4	34.3	32.8	32.2	33.4	32.3	32.7	32.0	30.1	30.2	31.5	234/121	91	+33	Hypertension. En- larged heart. Arteriosclerotic heart disease	Preop. L/R 24/13
308001	5/11/44†	94	37.61	33.98	35.3	35.8	34.5	34.3	33.9	33.8	34.2	33.1	31.9	32.3	35.1	190/100	104	+35		
M. 51																				
Average preopera- tive*		50	37.21	33.44	34.4	34.5	33.9	33.9	33.6	33.4	34.3	33.1	32.3	32.3	32.7	213/125	76	+ 5		
Average postopera- tive†		63	37.18	33.89	34.8	34.5	34.4	34.2	33.7	33.6	34.7	33.0	32.8	33.1	34.7	182/112	82	+ 1		
Standard deviations about the means preoperative		23	0.26	0.90	0.9	0.8	0.8	1.0	0.7	0.7	1.0	0.9	0.9	1.1	1.1	20/ 12	9			
Standard deviations about the means postoperative		25	0.23	0.40	0.3	0.6	0.4	0.5	0.6	0.4	0.3	0.5	0.9	0.5	0.4	12/ 12	10			
Smithwick Operation Followed by No Change in Blood Pressure																				
P. L.	3/ 1/42*	16	37.20	33.07	34.6	34.0	33.5	34.0	32.6	32.7	34.8	32.5	31.9	32.4	30.8	168/121	67	-22	Hypertension	Preop. 11 d. after L. L/R 32/17 Postop. 1 yr.
319076	3/30/42	22	37.11	32.97	34.2	34.1	33.3	33.0	32.1	32.2	34.4	32.4	31.3	32.0	34.3	170/119	65	-24		
M. 24	4/20/42	8	37.07	32.41	33.9	33.2	32.6	32.5	31.2	31.6	33.8	31.8	31.1	32.2	33.3	181/125	75	-24		
25	5/ 4/43†	13	37.06	32.80	35.3	34.3	33.1	33.0	31.3	31.3	28.5	33.0	31.0	33.3	34.0	186/128	64	-16		
C. N.	5/31/44*	71	37.38	33.92	35.1	35.0	34.9	34.4	34.1	33.7	35.4	33.1	33.4	31.9	32.9	140/ 85	66	+ 1		
386902	6/14/44	78	37.20	33.77	35.0	34.4	34.5	34.2	33.7	32.9	34.1	33.1	32.3	33.3	34.0	181/101	68	+ 5	Essential hyperten- sion. Enlarged heart	Preop. 12 d. after L. L/R 25/12
F. 42	6/27/44†	73	37.06	33.72	34.6	34.7	34.1	34.4	32.9	32.9	34.0	33.2	32.9	33.0	34.3	183/ 96	64	+ 1		
S. C.	5/27/44*	32	37.22	33.11	34.3	33.7	33.6	33.1	33.5	32.7	34.4	32.4	32.2	32.1	33.2	150/107	73	- 4		
384676	6/13/44	47	37.57	33.29	33.1	33.8	34.4	33.4	33.5	33.2	34.5	32.2	33.1	33.0	34.1	183/128	106	+10		
F. 33	6/28/44†	41	37.20	33.31	33.9	33.5	33.4	33.2	33.6	32.8	33.3	32.4	33.1	33.2	34.3	161/108	94	0		
I. R. S.	4/ 4/44*	16	37.23	33.17	34.7	34.1	32.9	32.8	32.9	33.0	34.6	32.0	32.8	32.8	33.5	182/118	71	- 4	Essential hyperten- sion	Preop. L/R 26/14
381016	5/18/44†	27	37.23	33.02	34.8	34.5	33.6	32.6	32.5	32.5	34.3	31.9	31.5	32.1	33.8	188/111	94	- 8		
F. 50																				
T. G.	1/ 5/42*	119	37.07	34.47	35.2	34.9	34.9	35.0	34.1	34.3	35.2	33.8	33.7	33.9	34.4	146/116	92	- 9		
311596	2/ 4/42	160	37.24	34.79	35.2	35.5	35.1	35.6	34.5	34.4	35.3	34.2	34.1	34.0	34.9	220/166	103	- 5		
M. 13	2/20/42	87	37.32	34.26	35.2	34.9	34.8	35.1	33.7	33.6	34.3	33.4	33.0	33.9	34.5	176/142	110	- 7		
	5/ 7/42†	28	36.89	33.22	33.4	33.5	33.5	33.5	32.9	33.1	33.3	32.6	32.9	33.1	33.6	153/114	78	-10		

Average preoperative*	51	37.22	33.55	34.8	34.3	34.4	33.9	33.5	33.3	34.9	32.8	32.6	33.0	157/109	74	- 8	
Average postoperative†	36	37.09	33.21	34.4	34.1	33.5	33.7	32.6	32.5	34.7	32.6	32.9	34.0	174/111	79	- 7	
Standard deviations about the means preoperative	40	0.32	0.56	0.3	0.9	0.9	0.8	0.6	0.6	0.4	0.6	0.8	1.2	15/ 13	8		
Standard deviations about the means postoperative	21	0.12	0.31	0.9	0.5	0.3	0.7	0.8	0.6	2.9	0.5	0.9	0.3	14/ 10	13		

Partial Sympathectomy Followed by Moderate Decrease in Blood Pressure

E. L.		37.24	32.70	33.8	34.0	33.5	33.3	32.0	32.7	33.4	32.0	31.4	31.3	32.4	220/130	-27		Preop.
233250	4/27/39*	37.12	32.61	33.4	34.2	33.8	33.3	32.5	32.8	33.2	31.0	30.9	31.4	32.4	214/112	+ 5		Preop.
F. 43	5/ 6/39	37.32	32.07	33.3	34.4	32.9	33.9	31.8	31.7	33.2	31.1	30.7	30.4	30.6		+17		10 d. after R.
	6/ 6/39†	36.97	33.32	34.0	34.4	34.3	34.1	32.5	33.3	33.9	32.6	32.0	32.4	32.9	196/105	- 4		R/L 29/12
M. N.	4/28/39*	37.39	33.53	34.3	34.4	34.4	34.5	33.7	33.8	34.2	33.5	32.7	31.2	32.5	230/130	+16		Preop.
231336	5/12/39	37.23	32.57	33.9	33.5	34.4	34.1	32.6	32.3	31.9	32.6	33.0	30.5	27.9	229/135	+ 9		11 d. after R.
F. 33	6/ 1/39†	36.95	33.61	34.4	34.0	34.5	34.3	33.0	33.8	34.7	32.7	33.3	32.1	33.7	200/132	- 1		R/L 31/15
A. R.	4/23/40*	37.11	33.49	35.1	34.6	34.6	34.5	34.5	34.1	34.4	33.3	33.4	31.9	29.6	187/124	-11		Preop.
249201	5/ 1/40	36.92	33.77	34.7	34.3	33.6	34.0	33.9	33.7	34.5	33.3	33.9	33.1	33.4	127/ 96	-11		Preop.
M. 40	5/10/40	37.37	32.46	34.9	35.2	33.5	33.5	33.2	33.5	34.1	31.6	31.3	29.9	26.4	158/117	- 7		7 d. after L.
	5/27/40†	37.12	33.06	34.5	33.9	33.8	33.6	33.8	33.9	34.2	33.0	33.4	32.1	27.2	149/104	-15		L/R 20/12
43	4/28/43	37.33	33.51	34.8	34.6	33.7	33.7	34.1	34.0	34.7	33.5	33.8	32.7	29.1	193/129	- 4		Postop. 3 yrs.
W. M.	2/ 6/39*	37.28	34.68	35.7	35.3	35.4	35.7	34.9	35.1	35.1	34.3	34.6	33.5	31.8	201/139	+22		Preop.
224740	2/ 8/39	37.25	34.66	35.6	35.2	35.3	35.5	35.0	35.0	35.3	34.5	34.5	33.3	32.5	196/135	+10		Preop.
M. 26	2/27/39	37.07	33.69	34.6	34.8	34.7	34.1	33.9	33.9	34.2	33.5	33.8	31.9	31.2	228/153	+ 5		11 d. after R.
	3/28/39†	37.09	34.32	35.3	35.3	34.6	35.1	34.5	34.4	34.7	33.2	33.8	33.7	32.4	177/136	-10		R/L 40/13
T. W.	2/29/40*	37.64	35.34	35.6	36.3	36.5	36.5	35.8	35.1	35.6	35.5	33.7	34.0	33.5	227/129	+22		Preop.
243332	3/12/40	37.55	34.96	35.8	36.1	36.0	36.2	35.6	34.9	35.2	35.3	33.4	33.3	33.1	202/124	+13		11 d. after L.
F. 39	3/29/40	37.56	34.69	35.4	35.6	35.7	35.8	34.9	34.5	35.1	35.0	32.5	33.0	34.0	213/119	+ 8		L/R 28/13
	5/ 3/43†	37.35	34.40	35.2	35.5	35.5	35.5	34.1	34.3	34.7	34.0	33.0	33.0	33.4	193/127	+19		Postop. 3 yrs.
Average preoperative*	97	37.33	33.95	34.9	34.9	34.9	34.9	34.2	34.2	34.4	33.7	33.2	32.4	32.0	213/130	+ 4		
Average postoperative†	78	37.10	33.74	34.7	34.6	34.5	34.5	33.6	34.1	34.4	33.1	33.1	32.7	31.9	183/121	0		
Standard deviations about the means preoperative	55	0.18	0.94	0.7	0.9	1.0	1.1	1.3	0.9	0.8	1.2	1.1	1.2	1.3	16/ 6			
Standard deviations about the means postoperative	44	0.56	0.50	0.6	0.7	0.6	0.7	0.7	0.4	0.3	0.5	0.6	0.6	2.4	19/ 14			

TABLE I—CONT'D

NAME HIST. NO. SEX AGE (YRS.)	DATE	PERIPH- ERAL BLOOD FLOW C.G./M ² / MIN.	RECTAL TEMPER- ATURE ° C.	AVERAGE WEIGHT- ED SKIN TEMPER- ATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS	TIME RELATION TO OPERATION
					° C.															
					1	2	3	4	5	6	7	8	9	10	11					
					° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.					

Partial Sympathectomy Followed by No Change in Blood Pressure																				
M. H.	11/10/39*	66	37.08	33.73	34.8	34.5	35.2	35.2	33.6	33.4	33.5	33.4	31.6	31.4	27.6	129/129	96	+ 8	Hypertension.	Preop.
250110	11/30/39	49	37.48	33.04	34.7	34.1	34.7	34.9	33.5	33.6	33.6	32.7	30.2	30.7	31.0	217/121	93	+ 9	Slight cardiac enlargement	16 d. after R. R/L 35/11
F. 33	12/19/39†	42	37.77	33.25	34.6	34.0	34.5	34.2	33.3	33.2	33.9	32.5	31.7	31.1	33.2	213/128	100	+15		
A. B.	2/14/40*	128	37.24	34.25	35.1	35.3	35.4	35.6	34.7	34.2	34.0	34.9	33.4	33.8	30.8	173/124	68	- 4	Malignant hyperten-	Preop.
256256	3/ 1/40	81	37.19	33.96	35.2	35.4	35.1	35.1	34.3	33.9	33.7	34.2	32.6	32.5	30.7	179/135	93	-13	sion. Enlarged	3 d. after L. L/R 27/13
M. 19	3/19/40†	48	36.93	34.01	34.9	34.8	35.1	35.2	34.0	33.8	34.0	34.1	33.0	33.2	31.0	171/121	65	- 3	heart. Mitral in-	
20	6/17/41	46	36.63	33.33	34.0	34.4	34.4	34.4	33.2	32.8	33.1	33.3	32.2	32.6	30.7	181/126	63	- 6	sufficiency. Mitral	
21	3/25/42*	49	37.12	33.81	34.5	35.0	35.2	35.1	34.1	33.6	33.7	33.9	33.1	32.8	29.3	196/127	59	0	stenosis.	Preop.
	4/15/42	52	37.11	33.77	34.6	34.8	35.0	34.7	34.1	33.5	34.2	34.0	33.4	32.3	30.1	175/121	80	- 5	Encephalopathy	11 d. after R. R/L 32/14
22	5/ 6/42†	53	36.96	33.27	33.4	34.0	33.8	33.8	33.1	33.1	34.0	33.3	32.5	32.7	32.0	180/132	72	- 2		Postop. 1 yr. Preop.
23	6/11/43	94	37.55	34.39	34.9	36.3	35.0	35.1	34.2	34.2	35.0	34.5	33.2	32.9	34.3	203/139	70	+ 5		
	6/16/44	88	36.99	34.24	34.6	35.2	34.3	35.2	33.9	33.6	34.8	34.0	32.9	33.2	34.9	205/141	73	+11		
Average preopera- tive*		81	37.15	33.93	34.8	34.9	35.3	35.3	34.1	33.7	33.7	34.1	32.7	33.0	29.2	196/127	74	- 1		
Average postopera- tive†		48	37.22	33.51	34.3	34.3	34.1	34.4	33.5	33.4	34.0	33.3	32.7	32.3	32.1	188/127	79	0		
Standard deviations about the means preoperative		22	0.07	0.25	0.3	0.4	0.1	0.2	0.5	0.4	0.2	0.6	0.8	1.0	1.3	18/ 2	17			
Standard deviations about the means postoperative		5	0.39	0.35	0.7	0.4	0.6	0.6	0.4	0.3	0.1	0.7	0.6	0.9	0.9	18/ 5	15			
Average of all pre- operative measure- ments		69	37.25	33.75	34.7	34.7	34.5	34.4	33.9	33.6	34.4	33.2	32.8	32.5	32.9	189/120	73	- 3		
Standard deviations about the means		41	0.27	0.77	0.6	0.7	0.9	1.0	0.8	0.8	0.8	1.0	1.2	1.0	2.0	28/ 13	9			
Average of all post- operative measure- ments		60	37.20	33.68	34.7	34.7	34.4	34.3	33.6	33.3	34.3	33.0	32.7	32.7	33.2	175/116	79	- 3		
Standard deviations about the means		32	0.86	0.55	0.5	0.6	0.6	0.8	0.8	0.8	1.2	0.9	0.8	0.9	2.0	30/ 18	12			

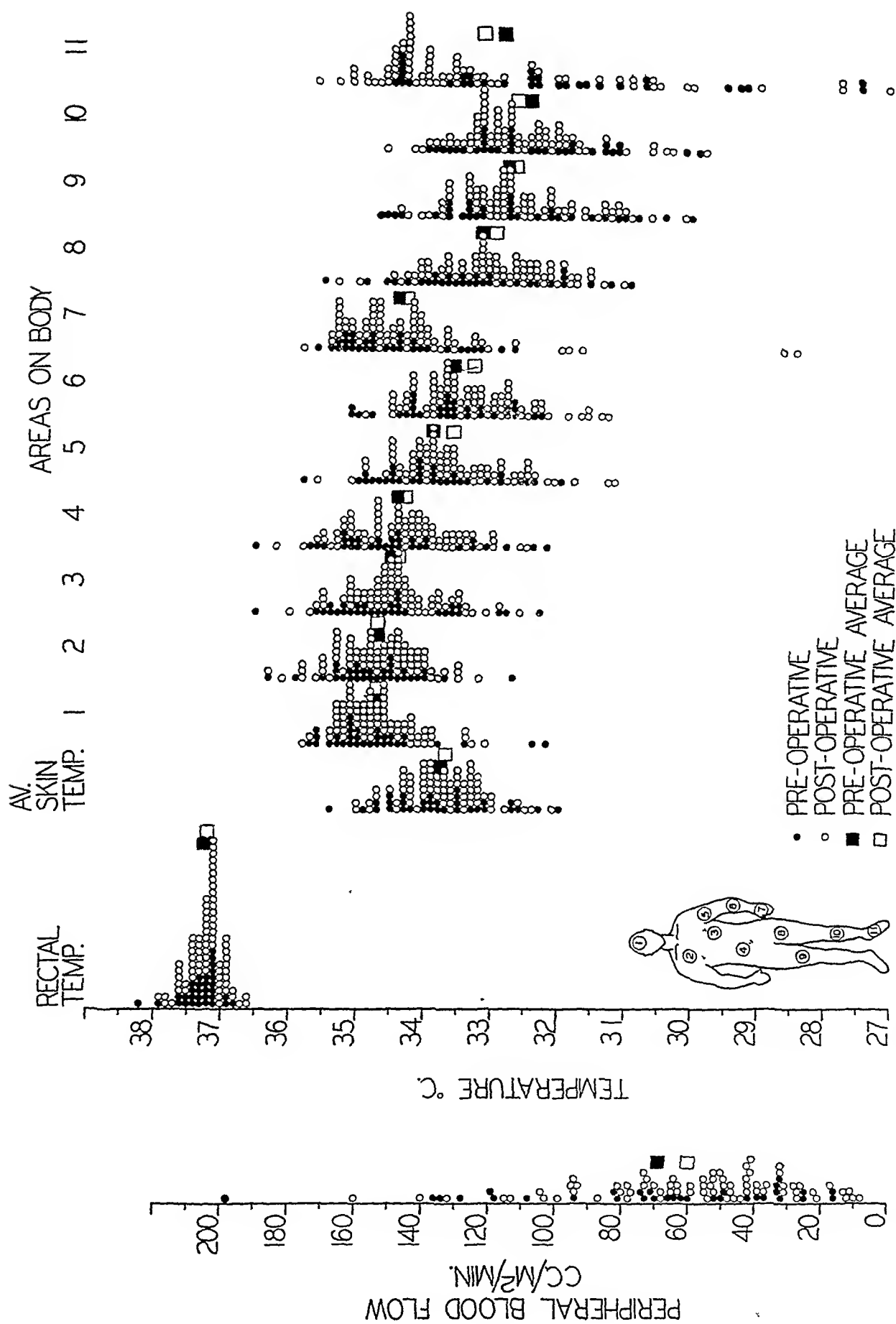


Fig. 2.—In this figure are shown all the preoperative (open circles) and all the postoperative measurements (closed circles) on all patients (Table I). The corresponding averages of all patients are shown in open and solid squares, respectively (for description, see text). If this chart is examined with the peripheral blood flow heading down, it is a series of frequency curves.

areas of the body except Area 2 (upper chest) rose, but the increases were not statistically significant. The greatest increase, a rise of 2° C., was in the feet (Area 11); this rise occurred consistently and was significant. The increase of 0.8° C. in the temperature of the leg (Area 10) was not significant. The peripheral blood flow rose from 50 c.c. to 63 c.c. per square meter per minute, which was statistically significant.

Observations Relating to Patients Subjected to the Smithwick Operation in Whom No Change in Blood Pressure Occurred.—Five patients, two men and three women, comprise this group (Table I, Fig. 2). The preoperative levels of blood pressure in this group was lower than in the other group, namely 157/109. After operation, the rectal temperature fell slightly, the average skin temperature fell, and the temperature of areas of the body from 1 to 9, inclusive, fell; these areas include the forehead (Area 1), the upper chest (Area 2), the lower chest (Area 3), the abdomen (Area 4), the upper arm (Area 5), the forearm (Area 6), the hand (Area 7), the upper thigh (Area 8), and the lower thigh (Area 9). The temperature of the leg (Area 10) increased only 0.3° C. and that of the foot (Area 11) only 1° C. as compared with a 2.2° C. rise in the group of patients whose blood pressure fell after operation. These changes are not significant. Decrease in peripheral blood flow from 51 c.c. to 36 c.c. per square meter per minute did not appear significant, though this group which includes only five patients is small for statistical analysis. In the five patients of this group the blood pressure rose after operation instead of falling; the average was 174/111 after operation as compared with 157/109 before operation.

Observations Relating to Patients Who Experienced Partial Sympathectomy in Whom Moderate Fall in Blood Pressure Occurred.—Five patients, two men and three women, comprise this group. The average blood pressure fell from 213/130 to 183/121 after operation. After operation (Table I, Fig. 2) no significant changes occurred in the rectal, average weighted skin, and local temperatures, or in peripheral blood flow. There was not the rise in temperature of the feet which was observed following the Smithwick procedure.

Observations Relating to Patients Having Partial Sympathectomy in Whom a Fall in Blood Pressure Did Not Occur.—This group comprises one man and one woman. A. B. was subjected to the more extensive procedure two years after the partial operation. After operation (Table I, Fig. 2) the only significant change was the rise of 2.9° C. in the temperature of the foot (Area 11).

DISCUSSION

Observations relating to peripheral blood flow have been made in patients before and after sympathectomy designed to lower the blood pressure. The Smithwick procedure was more effective for this purpose than was partial sympathectomy. The data have been analyzed so that the behavior of the peripheral blood flow could be related to the response to the operation.

In all the small groups of hypertensive subjects, the trend, before operation, was for the temperature of the upper part of the body to be warmer than normal, and for the temperature of the lower part of the body to be cooler than normal.²⁸

In those patients subjected to the Smithwick procedure in whom the blood pressure fell to normal after operation, the temperature of the upper part of the body fell after operation and the temperature of the lower part rose as much as 2.2°C . in the feet; the peripheral blood flow decreased; the rectal temperature, which was elevated, decreased; and the average weighted skin temperature decreased. The weighted fall in the upper part more than balanced the rise in temperature of the lower extremities. These temperature changes are shown graphically in Fig. 1. Before operation (open circles) the symbols representing the rectal, average skin, and the temperatures of Areas 1 to 8 are mostly at the upper part of the chart, while those of Areas 10 and 11 are mostly at the lower part. After operation (closed circles), the rubrics representing the rectal, average skin, and the temperatures of Areas 1 to 8 move down, but those representing the temperatures of Areas 10 and 11 move up. Though this is the trend, only the change in the foot temperature is of statistical significance. Before operation, in the group in which the Smithwick operation produced a moderate fall in blood pressure, the rectal temperature was slightly elevated, the average weighted skin temperature was slightly decreased, but the temperatures of the areas of the skin were essentially normal except for the lower thigh and leg which were cooler; the peripheral blood flow was decreased. After operation, the average weighted skin temperature rose as did the temperature of most of the areas of the body, the greatest rise, 2°C ., being in the feet. The peripheral blood flow rose.

Those in whom there was no fall in blood pressure after operation had, before operation, essentially the same characteristics in their measurements as did the preceding group. After operation there was a fall in rectal temperature; the average weighted skin temperature fell, as did the temperatures of the individual areas for the upper part of the body, with the exception of the feet in which the temperature rose 1°C . only. The peripheral blood flow decreased as would be expected with the lower skin temperature.

In those patients subjected to partial sympathectomy the peripheral blood flow decreased and the weighted skin temperature fell. Those in whom the lowering in blood pressure was moderate showed very slight fall in foot temperature, and those in whom the blood pressure was unchanged showed a rise in foot temperature.

Out of these observations no patterns appear which relate the amount of peripheral blood flow to the level of blood pressure following sympathectomy. The average weighted skin temperature rose or fell according to whether the peripheral blood flow increased or decreased after operation. There was, on the whole, rise in the foot temperature as a result of operation, the most marked increase being in those who had the more extensive operation (Smithwick) and in whom there was fall in blood pressure.

Fall in blood pressure to normal after the Smithwick operation occurred in six women but in only one man. When this group of six women is analyzed for the changes occurring after operation, they show the same general trends as the group as a whole, namely fall in peripheral blood flow, fall in rectal temperature, fall in average weighted skin temperature, and fall in temperature of the upper part of the body and rise in temperature of the lower part of the

body. From these observations we could not detect any characteristics which set those patients apart from those who failed to experience a fall in blood pressure.

In those patients subjected to the Smithwick procedure and to partial sympathectomy, all the measurements before operation were averaged and compared with the corresponding estimations after operation (Table I, Fig. 2). Likewise all the preoperative as well as the postoperative measurements of all patients subjected to any form of sympathectomy were averaged. The changes for the entire group of patients are less marked, because the changes shown in those groups in which marked changes occurred are pulled out of line by those in which no changes occurred. The trends, as shown in the frequency diagram (Fig. 2) are, however, essentially the same as in the smaller groups, but are not of statistical significance.

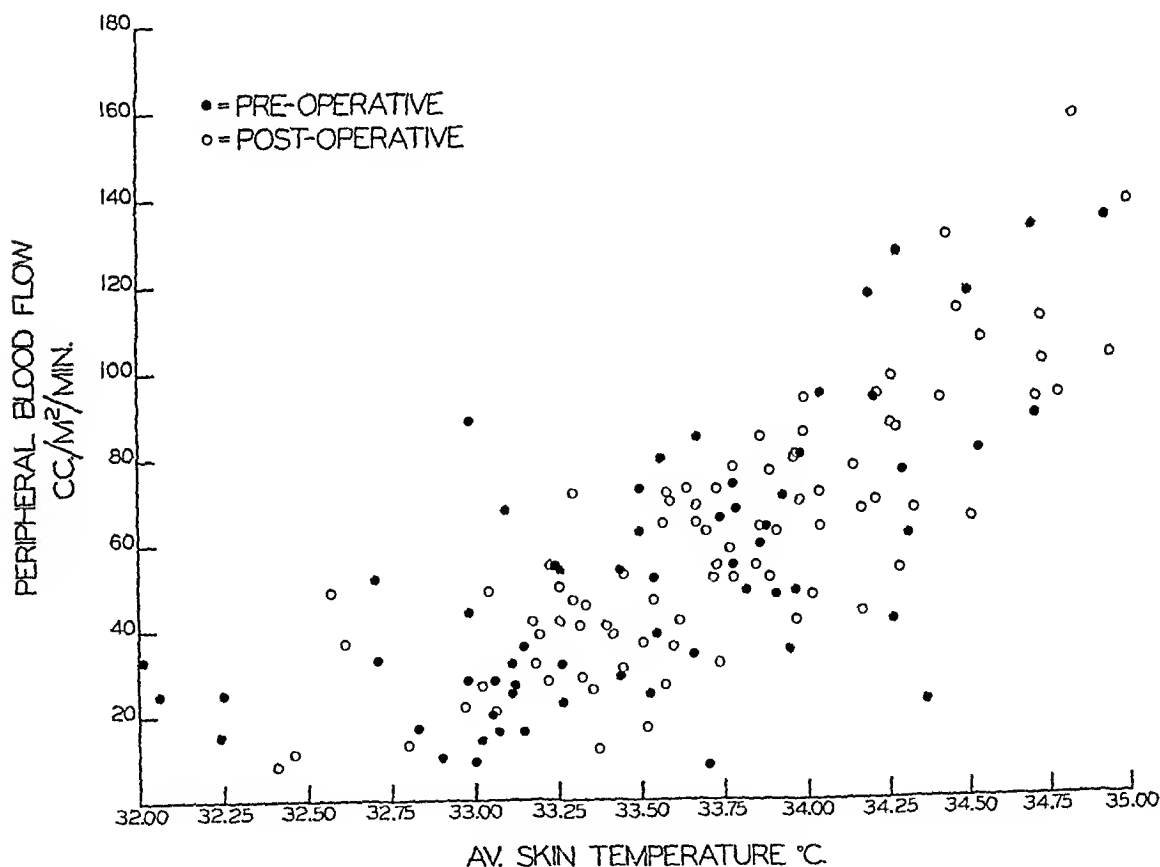


Fig. 3.—In this figure all the peripheral blood flows of all patients (Table I) are plotted against the corresponding average skin temperatures before (closed circles) and after (open circles) operation. A linear relationship is apparent in that the higher average skin temperatures were associated with the higher peripheral blood flows.

The colder feet and lower parts of the body in hypertension may be due to increased vasoconstriction in these regions and in the splanchnic area, which is relieved by splanchnic resection. The marked rise in foot temperature is what is to be expected from including the section of the second lumbar ganglion in the operative procedure.

The data relating to the basal metabolic rates are of interest. Those patients in whom the blood pressure fell to normal (Smithwick) showed a fall in the basal metabolic rate from +3 per cent to -7 per cent, a fall of 10 per cent; those showing slight fall in blood pressure (Smithwick and partial sympathectomy) showed a fall in rate of 4 per cent; and those whose blood pressure was not altered (Smithwick and partial sympathectomy) showed no change in the basal metabolic rate.

In the group of hypertensive patients considered in this paper, there is a linear relationship between peripheral blood flow and average weighted skin temperature before operation (Fig. 3), just as there was in the larger group already reported.¹ This relationship is maintained after operation, but the correlation is even more striking and fewer points fall outside the zone showing the closest correlation (Fig. 4).

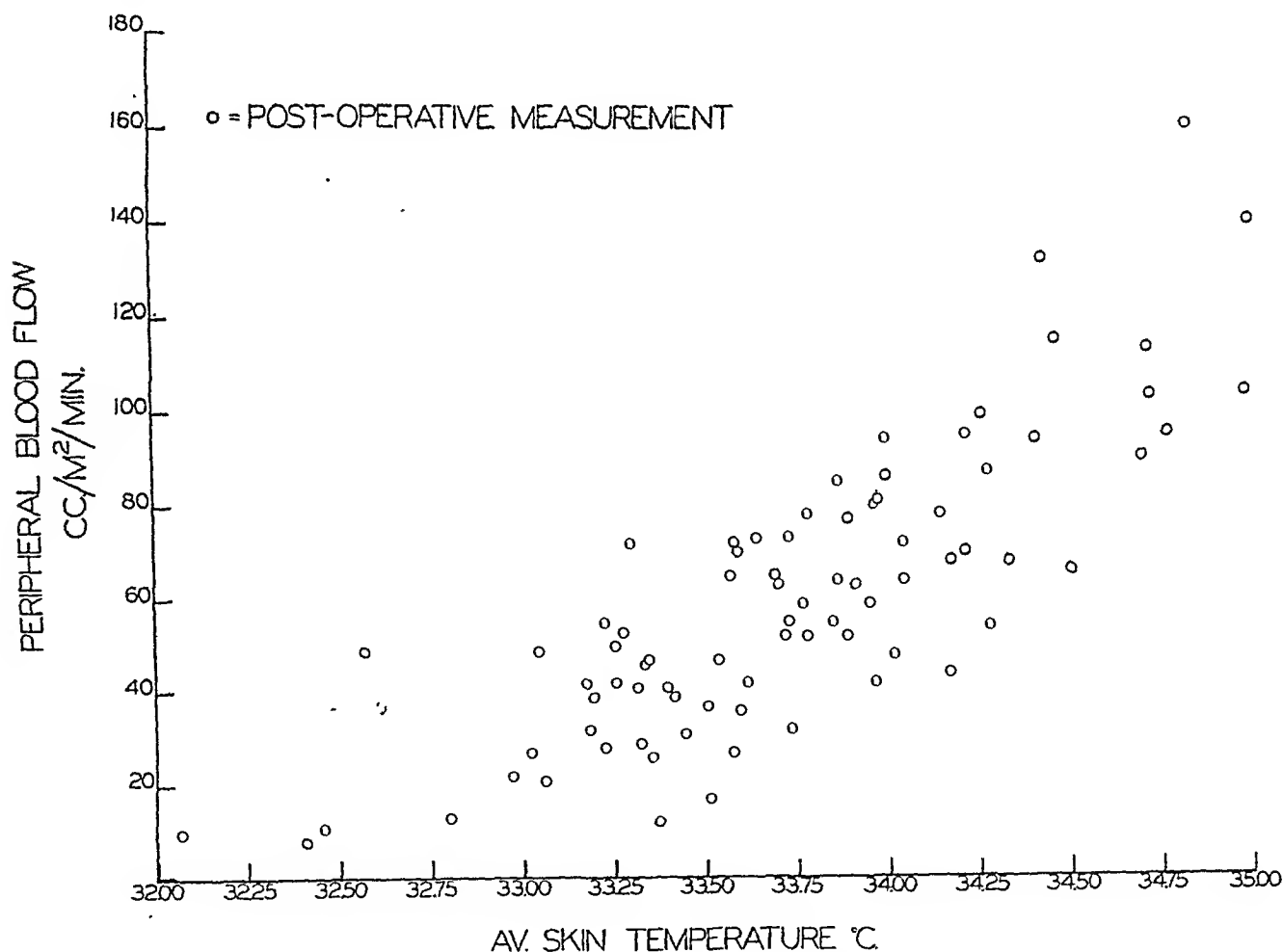


Fig. 4.—In this figure all the postoperative measurements of peripheral blood flows of all patients (Table I) are plotted against the corresponding average skin temperatures (Table I) revealing a very close correlation. Most of the points which were out of line with this correlation in Fig. 3 were in the preoperative measurements of the patients.

SUMMARY

The peripheral blood flow has been measured by a modification of the method of Hardy and Soderstrom in patients with arterial hypertension before and at intervals after splanchnic resection, undertaken with the intent of lowering the blood pressure. In addition observations were made of the skin and

rectal temperatures. In 19 patients the Smithwick procedure was carried out, and in seven operated upon earlier, the less extensive operation was done. The following facts emerged:

1. In these patients the Smithwick procedure was more effective in lowering the blood pressure than the less extensive splachnic resection.

2. Since the objective of the operation is to lower the blood pressure, the groups in which this occurred are of special interest with respect to peripheral blood flow. The most marked differences in the observations made before and after operation were recorded in the group in which the blood pressure fell to normal after operation. The peripheral blood flow decreased, the rectal temperature fell, the average weighted skin temperature fell, the temperature of the upper part of the body fell; the temperature of the lower part of the body, especially of the feet, rose. The effects were less in those with less marked fall in blood pressure or without change in blood pressure.

3. There was, however, no pattern discernible in the individual peripheral blood flows when these were analyzed in relation to the effect of the surgical procedure either in those in which the blood pressure fell to normal or in those showing less benefit from the operation.

4. The peripheral blood flow in hypertension bears a linear relationship to the weighted skin temperature. This relationship is especially close after splenchnic resection.

5. In those patients exhibiting the most marked lowering of blood pressure after operation, the average skin temperature fell after operation. The temperature of the upper part of the body, which before operation was warmer than normal, fell; the temperature of the feet, which before operation was cooler than normal, rose after operation. The elevated rectal temperature in hypertension falls after operation.

6. In those patients showing a fall in blood pressure to normal after operation, the mean basal metabolic rate decreased 4 per cent, and in those whose blood pressure was not lowered, no change in the mean basal metabolic rate occurred.

7. While the peripheral blood flow is, on the average, lower in hypertensive than in normal subjects,¹ there are wide ranges, and the differences are not significant. The level of blood pressure has no relation to peripheral blood flow either where the blood pressure is high or in the same patient after restoration of normal blood pressure.

It is likely that the mechanism, whatever it may be, which is responsible for the elevation of blood pressure in hypertension is also responsible for the differences in local skin temperatures which hypertensive patients exhibit when compared with normal individuals.

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MYOCARDIAL COMPLICATIONS OF CUTANEOUS DIPHTHERIA

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THE diagnosis of cutaneous diphtheria was made in 140 American soldiers admitted to a United States Army General Hospital in the India-Burma Theater during the period from July through December, 1944. The myocardial complications observed in these patients are considered in this report. Data are presented with reference to the incidence, predisposing factors, time of onset, duration, symptomatology and course, physical findings, electrocardiographic studies, associated neuritic complications, treatment, and ultimate disposition of these patients. None of the patients of the cutaneous diphtheria series who developed a cardiac complication had had clinical evidence of faucial diphtheria.

A communication dealing especially with the dermatological aspects of cutaneous diphtheria, including data with reference to the epidemiology, incidence, predisposing factors, description of the lesions, laboratory findings, treatment, and ultimate results, is to be published.¹ A separate report of the neurological complications of the disease is also to be published.²

The cases of cutaneous diphtheria considered in this report occurred almost exclusively in combat soldiers who had been evacuated during or after a strenuous campaign fought in jungles, marshes, and foxholes during the wet monsoon in Burma. Wet feet, poor foot hygiene, multiple minor abrasions, and insect and leech bites were undoubtedly important predisposing factors to the development of the cutaneous lesions. These lesions, which are described in detail elsewhere,¹ were ulcerative, usually with a membrane or a leathery, black, adherent, inlaid crust. The lesions were usually multiple, and predominantly affected the extremities. They were extremely resistant to treatment, and in many instances persisted for many weeks or months.

Although diphtheria was early suspected as the cause of the skin lesions, conclusive laboratory proof was not obtained until several weeks later. Organisms having the morphologic appearance of Klebs-Löffler bacilli were recovered in approximately 80 per cent of the 109 patients in whom the skin infection was still active at the time of admission, but at first the fermentation reactions appeared to indicate that these organisms were not diphtheria bacilli. Later, however, a change was made in technique with the result that virulence-positive Klebs-Löffler bacilli were recovered in 26 of the last 38 cases.

Neurological complications, described elsewhere,² developed in 43.5 per cent of these patients. They first appeared as early as the twenty-third day of the skin lesions or as late as the one hundred fifty-eighth day; the

average onset occurred at about the seventieth day. They varied in intensity from slight visual blurring, slight tingling of the extremities, or slight muscular weakness to extensive generalized paralysis with muscular wasting. Recovery was usually slow, averaging about one hundred days, but the ultimate prognosis was excellent.

A severe myocarditis, with rapidly fatal outcome, occurred as a complication in one of the first patients admitted in the epidemic. During the same week a similar fatality occurred in a near-by hospital. As a result, tremendous respect was engendered for this potentially lethal complication of what was otherwise an essentially benign, although prolonged and incapacitating disease. Consequently, in all patients in whom the diagnosis of cutaneous diphtheria was suspected, every effort was made to prevent the development of a cardiac complication or, if this was impossible, to detect and treat it at the earliest possible stage of development. With these objectives in view, all patients in whom the diagnosis of cutaneous diphtheria was suspected were isolated at complete bed rest as patients of the dermatology section, where local therapy was given. The policy with respect to the administration of antitoxin was at first poorly defined, but as soon as we became certain that we were dealing with cutaneous diphtheria in epidemic proportions, a definite policy for the administration of antitoxic serum was established: 20,000 to 40,000 units of diphtheria antitoxin were promptly administered to all patients in whom active cutaneous diphtheria was diagnosed clinically. Contrary to other reports, we are convinced that this disease can be accurately diagnosed by an experienced dermatologist, particularly in the height of an epidemic. As soon after admission as feasible, the patients were examined for any evidence of cardiac disease, and an electrocardiogram was taken. Thereafter, tracings were repeated every ten to twenty days until the lesions had become definitely inactive. Any patient who exhibited symptoms, signs, or electrocardiographic changes suggestive of cardiac involvement was observed especially closely and was studied frequently with the electrocardiograph. When cardiac involvement was definitely diagnosed or considered probable, the patient was continued at bed rest until all evidence of the cardiac complication had disappeared.

Myocarditis: Incidence, Time of Onset, Duration.—In the 140 patients with cutaneous diphtheria, myocardial complication was diagnosed as a certainty in four, one of whom died, and was considered probable in three others. The incidence was 5 per cent. In several additional patients it was considered possible that a minimal myocarditis had occurred, but the diagnosis could not be definitely established.

The earliest appearance of an electrocardiographic abnormality was on the twentieth day after the onset of the cutaneous lesions. In the patient who died on the forty-first day of his cutaneous disease, symptoms of cardiac disease first appeared about the thirty-eighth day. In another patient, the myocarditis was first diagnosed as late as the sixtieth day, although it may have been present for some time before this, inasmuch as the patient was not admitted to the hospital until the fiftieth day, had no cardiac symptoms, and did not have an

electrocardiogram taken until the sixtieth day. In general, the period of the fourth to the seventh week of the cutaneous diphtheria appeared to be that in which myocarditis developed, if at all.

The duration of the myocarditis ranged from twenty-eight to fifty days in those in whom the diagnosis was considered probable, and from sixty to ninety days in those in whom it was certain, excepting, of course, the one patient who died four days after the onset of symptoms. Cardiac abnormality did not persist beyond one hundred forty days from the onset of the cutaneous lesions in any patient.

Clinical Symptoms and Signs.—With few exceptions, symptoms were by far more frequent and more striking in those patients who did not have any evidence of organic cardiac disease than in those who had real cardiac complications. Typical cardiac neurosis phenomena, such as palpitation, tachycardia, stabbing precordial pains, and tachypnea, occurred with great frequency on the cutaneous diphtheria wards, especially after the death of the one patient. Of the seven patients in whom the diagnosis of myocarditis, definite or probable, was made, four had no symptoms which could be considered as cardiac in origin. Had these patients been allowed activity, it is quite possible that symptoms would have appeared. Of the other three, two complained of dyspnea and faintness upon slight exertion. The third patient, the one who died, first complained of aching right-sided abdominal pain with nausea and some breathlessness on exertion. These symptoms increased but were not incapacitating or severely distressing until eighteen hours before death when the discomfort extended upward into his chest as a steady dull pain; he began to vomit profusely, became very dizzy, and collapsed beside his bed. In spite of rest, morphine sedation, and oxygen, dyspnea and faintness persisted until death. It is interesting, and probably significant, that palpitation was never a symptom in any patient with myocarditis.

In the patient who died, whose symptoms have been described, the most striking physical sign was extreme pallor, despite a completely normal hemoglobin. The patient appeared moderately dyspneic; the neck veins were engorged, and the liver was enlarged and tender. There was no definite evidence of cardiac enlargement; precordial pulsation was not visible. Although the cardiac sounds were barely audible, there was a distinct gallop rhythm. The pulse was extremely feeble with a rate of 110. The systolic blood pressure was 60 mm. Hg; the diastolic pressure could not be determined.

In the other six patients, the physical signs were not striking. Tachycardia was absent; the heart rate at rest did not exceed 90 beats per minute. Two of the patients had occasional extrasystoles. The blood pressure was below 100, systolic, in only two instances; a pressure of 90/50 was the lowest reading obtained. The neck veins were not engorged. The heart was not enlarged on physical examination in any of these patients, although in one x-ray films showed slight but definite enlargement. Later the heart became normal in size. Precordial pulsations and cardiac sounds were definitely feeble in two of the patients; in the others they were normal. No murmurs or friction rubs were heard.

Laboratory findings were generally normal. A leucocytosis of 22,000, predominantly polymorphonuclear, was present on the day of death in the one patient. In the others the leucocyte count was normal; if any slight elevations were present they could be accounted for on some other basis. Sedimentation rates, taken on five of the seven patients, were normal.

Autopsy Findings.—At post-mortem examination of the one patient who died, the heart was flabby and slightly dilated. The pericardium contained 100 c.c. of straw-colored fluid. The epicardium, endocardium, and pericardium were speckled with many petechial hemorrhages. The myocardium was pale brown with grayish streaks. Microscopic examination revealed extensive fragmentation and disintegration of the muscle fibers, with degeneration, nuclear changes, and interstitial cellular infiltration, predominantly lymphocytic.

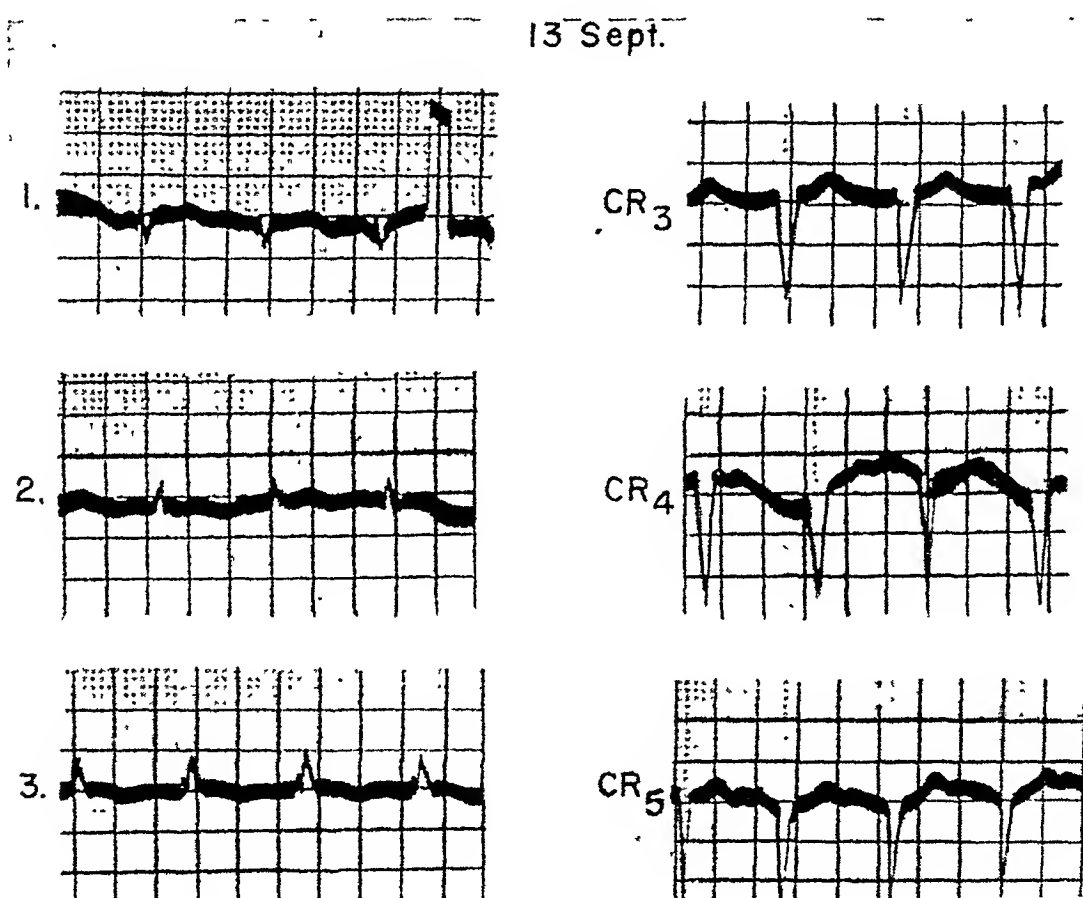


Fig. 1.—Definite myocarditis. Onset of cutaneous diphtheria August 3. Severity of lesion graded as 4 plus. There was no neuritis. Antitoxin was not given. The onset of cardiac symptoms was September 10. These consisted of abdominal pain, dizziness, dyspnea, vomiting, chest pain, and collapse. Death occurred on September 13. The electrocardiograph showed a rate of 110, with a regular rhythm. The P waves cannot be definitely identified. The QRS complexes in the limb leads were of low voltage and slurred. There were deep Q waves in all chest leads. The T waves are of low amplitude. The electrocardiographic diagnosis was "abnormal tracing, probably indicative of myocarditis."

Electrocardiographic Findings.—The electrocardiograph provided by far the most reliable and, in four instances, the only means of establishing the diagnosis of diphtheritic myocarditis. In all, 381 tracings were taken in the study of the 140 patients in whom the diagnosis of cutaneous diphtheria was made; in addition, tracings were taken on several patients with ulcerative skin lesions but in whom the diagnosis of diphtheria was ultimately excluded.

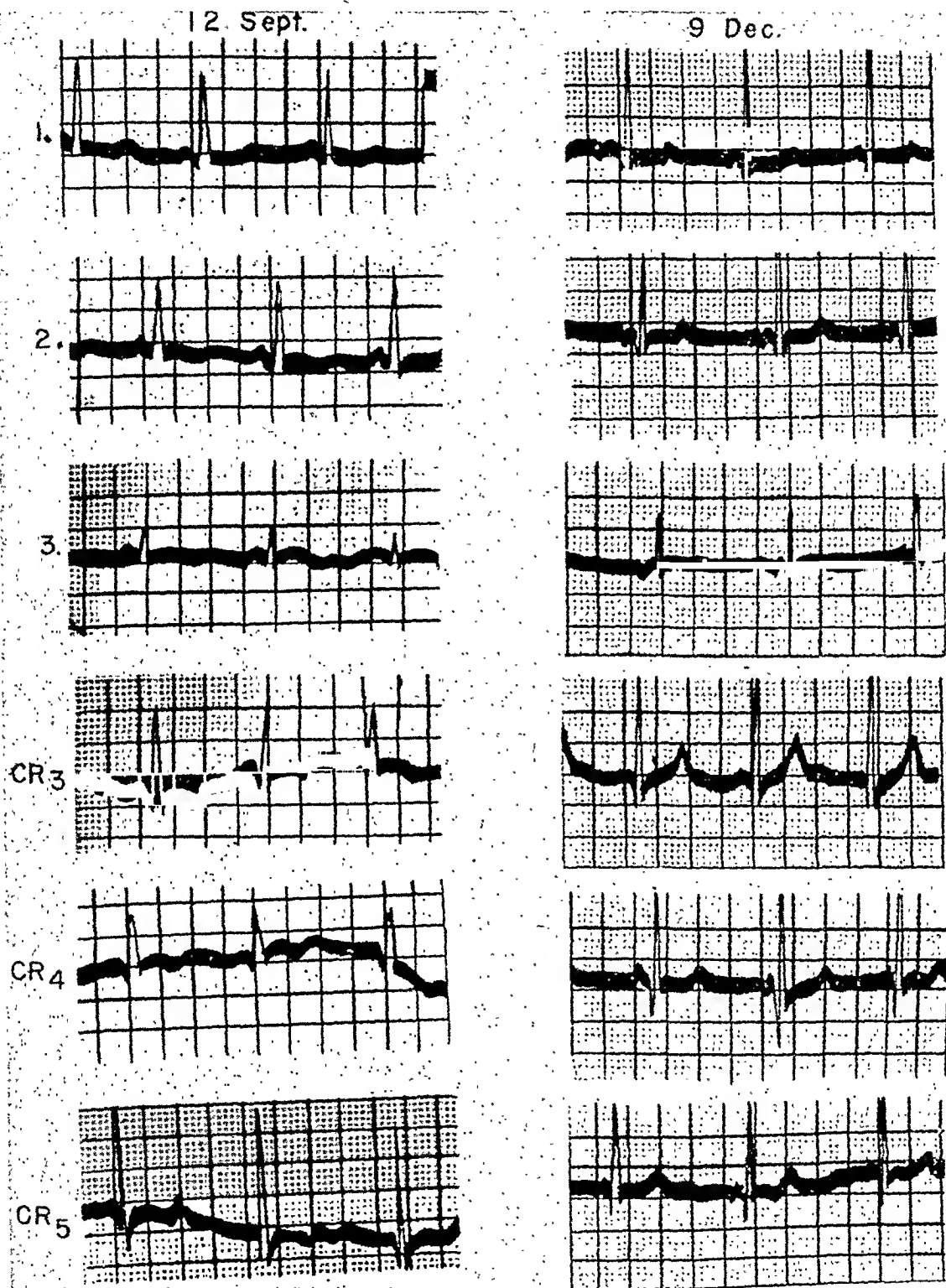


Fig. 2.—Definite myocarditis. Onset of cutaneous diphtheria July 5. Severity of lesions graded as 4 plus. Neuritis developed on the fifty-sixth day. The duration was one hundred forty-five days. Antitoxin was not given. Cardiac symptoms set in about the fiftieth day and consisted of dizziness and dyspnea. The electrocardiograph showed a rate of 75 to 85, with a nodal rhythm. The P-R interval was 0.08 to 0.11 second. There were intermittent inversions of the P waves in all leads. There were minor changes in the amplitude and configuration of the QRS complexes in serial tracings. The RS-T segments were slightly depressed in Lead I. The T waves were inverted in Leads II and III and the chest leads. In later tracings (e.g., December 9) the T waves became upright.

From an analysis of these tracings, several conclusions could be drawn: (1) Tachycardia was not an important feature. (2) Extrasystoles were observed no more frequently than one would expect in a group of normal individuals. (3) P-R interval prolongations above 0.20 second were not observed in any patient in

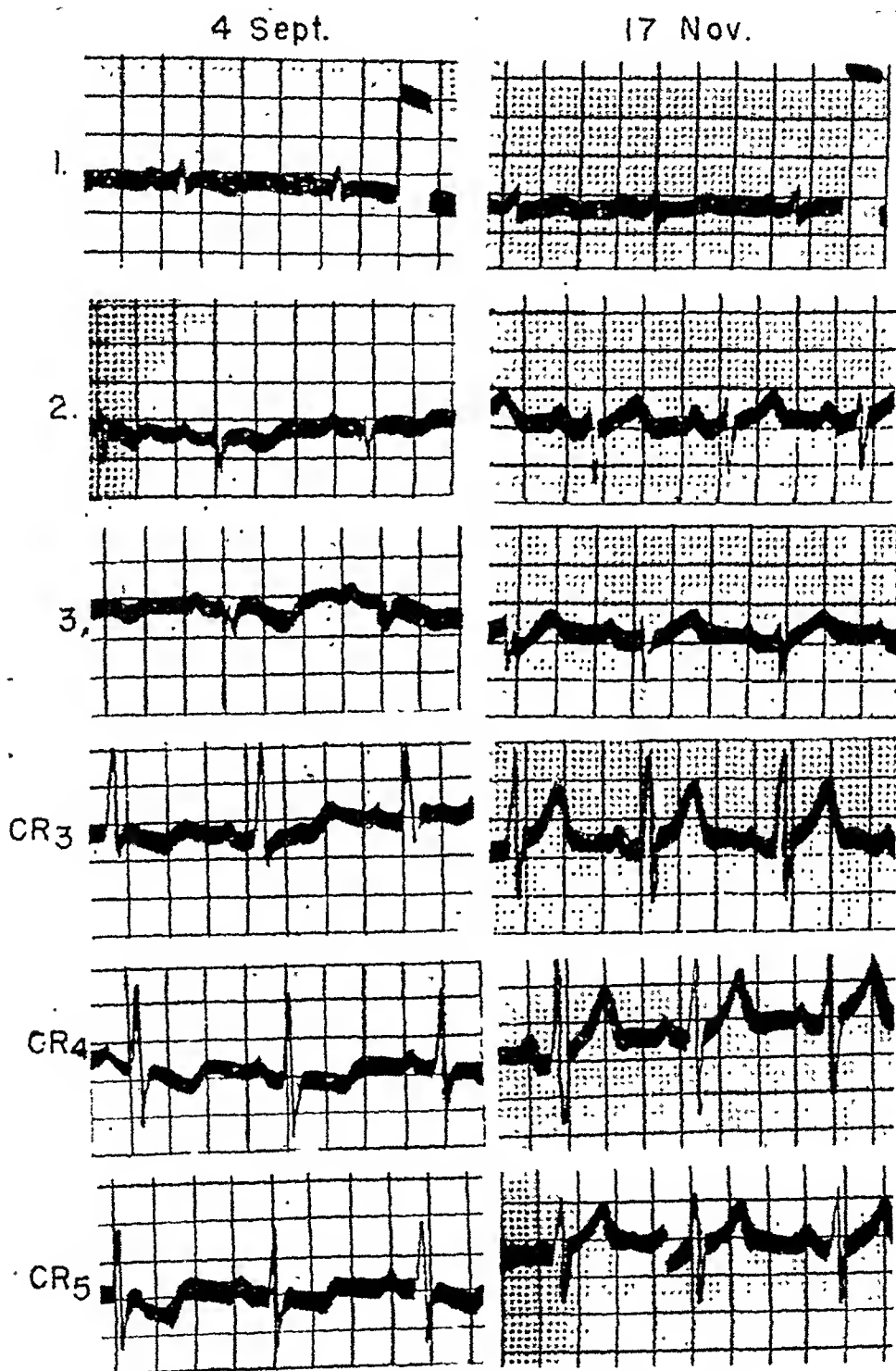


Fig. 3.—Definite myocarditis. Onset of cutaneous diphtheria July 1. Severity of lesions graded as 4 plus. Severe neuritis set in on the fifty-fourth day and lasted one hundred eighty-four days. No antitoxin was given. Cardiac symptoms appeared on the fifty-sixth day and consisted of dizziness and dyspnea. On September 4 the electrocardiograph showed a rate of 80, with a sinus rhythm. The P-R interval was 0.16 second. The QRS complexes were of very low amplitude. The T waves were inverted in all leads. The amplitude of the QRS complexes showed a progressive increase. On November 17 the T waves became upright in all leads.

whom the diagnosis of myocarditis was made, and in these patients the P-R interval did not tend to change significantly as recovery progressed. In two patients with no other evidence of myocardial abnormality, a P-R interval of 0.24 second was found. These patients were considered to have possible myocardial complication. Tracings were taken repeatedly. After a number of weeks, despite the persistence of the long P-R interval, one of them was reconditioned and sent to duty; the other was reassigned on neuropsychiatric grounds.

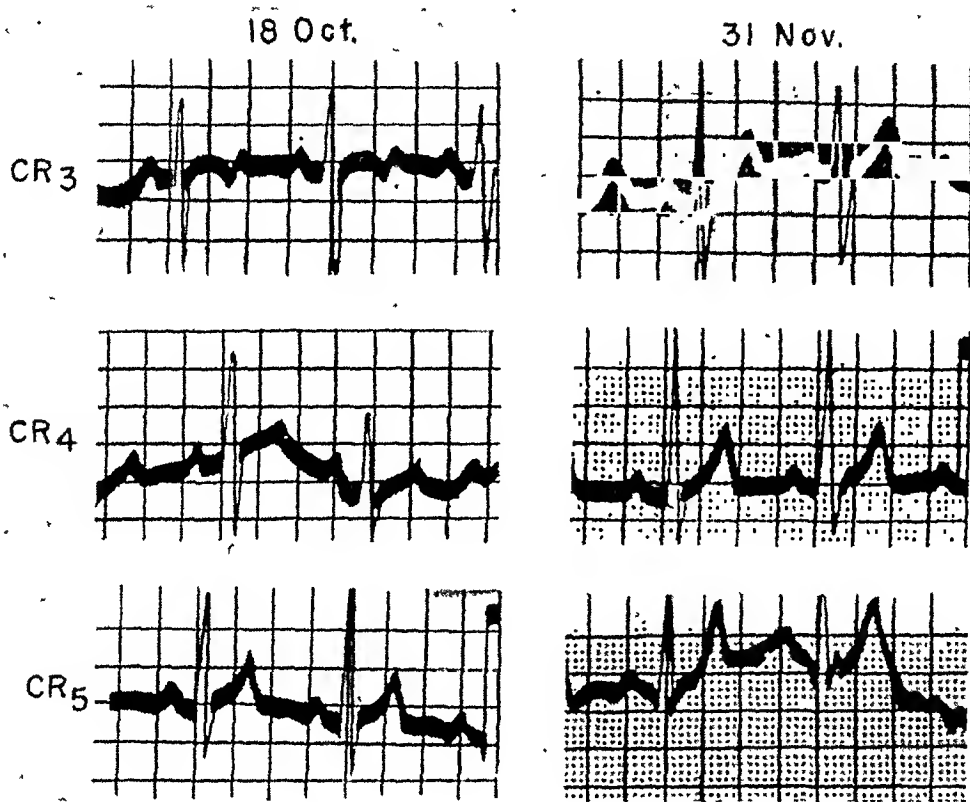


Fig. 4.—Probable myocarditis. Only the precordial leads are shown. Onset of cutaneous diphtheria September 8. Severity of lesions graded as 4 plus. There was no neuritis. Antitoxin was not given. There were no cardiac symptoms. The T waves in CR₃ were inverted in the first tracing, made on October 6 (twenty-eighth day). T-wave changes were most pronounced on October 18, less marked on November 8, and normal on November 24 (seventy-fifth day). T₁ was flat in the tracing of October 6 and became progressively higher during the period of the return to normal of the T waves in CR₃. The tracing was otherwise normal. The duration of electrocardiographic abnormality was forty-seven days.

We doubt that this finding was a manifestation of diphtheritic myocarditis. In the patient who died, P waves could not be definitely identified. One patient with definite myocarditis had a consistently short P-R interval with intermittent P wave inversion in all leads. (4) Abnormalities in the QRS complex were not striking. The amplitude was a little low in some instances and pronouncedly so in the patient who died. He also had very abnormal QRS complexes in the chest leads. Intraventricular conduction defects were not observed. (5) The most marked abnormalities were in the T waves, especially in Lead CR₃. Depression or frank inversion of the T wave in this lead was the one consistent finding, occurring in all of the patients in whom the diagnosis was made with the exception of the one who died. Figs. 1, 2, 3, and 4 are representative tracings from the patients in this series.

Criteria for the Diagnosis of Definite or Probable Myocarditis.—The diagnosis of myocarditis was considered certain in those patients in whom definite electrocardiographic abnormalities were observed in repeated tracings, with subsequent progressive changes toward normal. In three of the four patients so diagnosed there were corroborating clinical evidences of myocardial disease. Myocarditis was considered probable in patients in whom a definite and characteristic abnormality was observed in one tracing only, or in whom the electrocardiographic findings were highly suggestive of abnormality and showed progressive changes toward normal in repeated tracings. Clinical evidence of myocarditis was not present in these patients. Myocarditis was at first considered possible in a large number of patients, either on the basis of suggestive symptoms, tachycardia, or electrocardiographic findings (extra systoles, axis deviation, Q waves in Leads II and III, etc.) which suggested the possibility of abnormality. In most instances, the persisting and unchanging nature of these findings beyond the period when true myocarditis could be considered possible served to rule out organic cardiac disease. In seven patients, however, the possibility that a minimal myocarditis had been present could not be entirely excluded.

Relation of the Severity of the Cutaneous Disease to the Development of Myocarditis.—The 140 cases were graded according to their severity, depending upon the number and size of the cutaneous diphtheria lesions. Table I indicates the grade of severity of the cutaneous lesions in each of the patients with definite or probable myocarditis. It is apparent that definite myocarditis developed only in patients in whom the cutaneous disease was severe. In the patients with probable myocarditis the correlation is not so clear as in those with definite myocarditis.

TABLE I. THE SEVERITY OF THE SKIN LESIONS AND THE DEVELOPMENT OF MYOCARDITIS

Severity of skin lesions	4 plus	3 plus	2 plus	1 plus
Total number of cases	18	34	38	50
Definite myocarditis	3	1		
Probable myocarditis	1	1	1	

The Development of Neuritis With Relation to Myocarditis.—In the group of four patients in whom the diagnosis of myocarditis was definite, all but one, the patient who died, had neuritis, either severe or moderately severe. In two patients the symptoms of neuritis appeared at about the same time or slightly before there was evidence of cardiac involvement. In the third, neuritis had been present for twenty-eight days before the myocarditis was diagnosed on the sixtieth day of the cutaneous disease. In the group of three patients in whom the diagnosis of myocarditis was considered probable, only one developed neuritis, the onset of which occurred after the electrocardiographic abnormalities had disappeared. Thus, when myocarditis developed in cutaneous diphtheria, neuritis usually accompanied, preceded, or followed it.

Prevention and Treatment of Cardiac Complications.—In regard to these factors, we started with certain assumptions, and at the termination of the study our information had not greatly increased. For example, it was reasonable to

assume that any local or general therapeutic measures which would reduce the severity and duration of the cutaneous lesions would also reduce the frequency of the complications. These therapeutic methods are discussed in detail elsewhere.¹ It may be stated in brief that the most important factors were rest, local hygiene, and the prompt injection of antitoxin. A variety of local medications as well as systemic sulfonamides and penicillin were tried with indifferent results.

Of the seven patients who developed definite or probable myocarditis, only one had received antitoxin. This was a patient in whom the diagnosis of probable myocarditis was made only two days after the serum was injected. Despite this observation, no conclusion regarding the direct efficacy of antitoxin as a prophylactic agent can be drawn; many other considerations were involved. In the early cases, in which antitoxin was rarely given and limitation of activity was not enforced, the skin lesions were generally much more severe than the later cases in which treatment was noneffective; it was from this early group that six of the seven cases of myocarditis were derived. Likewise, myocarditis was never seen to develop in any patient after he had been restricted to bed; but for the same reasons, the virtue of this measure is difficult to assess.

Six of the seven patients with myocarditis recovered. The only therapeutic measure employed was bed rest until all evidences of abnormality had disappeared. None of these patients at any time appeared to be in serious danger from his cardiac disease; therefore, a conservative policy seemed justified and experimentation contraindicated. In the patient who died, the diagnosis was not made until about eighteen hours before death; bed rest, morphine, and oxygen were the measures used, but in view of the condition of the myocardium at autopsy, it seems doubtful that any therapy instituted at that late date would have influenced the outcome.

Ultimate Disposition.—Of the four patients in whom the diagnosis of myocarditis was definite, one died, one was reassigned to noneombat duty, and two were returned to the United States, primarily because of neuritic rather than cardiac complications. Of the three patients in whom the diagnosis was probable, one returned to full combat duty, one was reassigned to noncombat duty because of indolence of his skin lesions, and one was returned to the United States for reasons unrelated to his diphtheria. In all, no patient was confined to the hospital more than one hundred fourteen days for cardiac study or treatment; some remained longer, but for other reasons.

Discussion of the Management.—At the beginning of the epidemic we were not sure that we were dealing with cutaneous diphtheria. The dermatologist had suspected the possibility, yet all cultures had been negative. The death of a patient from a cardiac complication immediately focused our attention on the etiology, and gave rise to a strict set of rules for management and careful cardiac study of all cases. Although there is a great deal of literature on postfaucial diphtheritic myocarditis, very little information was available to us about the cardiac complications of cutaneous diphtheria. Nothing was known concerning the incidence, time intervals, correlation with severity of cutaneous lesions, or

relation of cardiac to neuritic complications. It was the general impression that antitoxin would be of little or no benefit except in the earliest stages of the skin disease.

As a result of our experience with 140 cases, the following impressions have been formed regarding cardiovascular management:

1. Patients in whom the diagnosis of cutaneous diphtheria is suspected should be immediately evacuated to a general or station hospital where adequate facilities for isolation, treatment, and study (including electrocardiography) are available.

2. Among the patients whose skin lesions were mild or minimal, prolonged confinement to bed resulted in more psychological and physical disability than was warranted by the potential danger of myocarditis. This selected group should be given freedom of the ward, cardiac symptoms should be carefully investigated, and tracings should be taken about every two weeks until three weeks after the cutaneous lesions have begun to heal. If no evidence of abnormality is then found, further cardiac study is unnecessary.

3. Patients with severe cutaneous diphtheria should be confined to bed and closely observed. Tracings should be made every week or ten days until about seven weeks after the onset of the lesions. Periodic tracings should be made for an even longer period if the activity of the cutaneous lesions is unusually prolonged. If at that time there is no evidence of myocarditis, activity may be resumed. A final tracing should be taken at about the tenth week.

4. In regard to the use of antitoxin, further information is needed. The possibility has been considered that large doses (200,000 to 400,000 units) might have more evident beneficial effects than doses of 20,000 or 40,000 units.

Comparison With the Myocardial Complications of Faucial Diphtheria.—The myocarditis we have observed as a sequel to cutaneous diphtheria resembles that which complicates the faucial form in several respects. In either instance the signs and symptoms of severe myocarditis are similar and dramatic, but in the milder forms are not striking.^{3-5, 8} When death does not occur in the acute phase of the complication, the prognosis for ultimate complete recovery is excellent.⁶ The pathologic findings in our fatal case resembled those described in the myocarditis of faucial diphtheria.^{7, 8} It is of especial interest to compare our series of 140 cases of cutaneous diphtheria with the series of 140 cases of faucial diphtheria which Burkhardt, Eggleston, and Smith⁸ followed with especial reference to cardiac and neurological complications. Twenty-three of their patients developed T-wave changes, principally during the second and third weeks of the illness. Similar T-wave changes developed in six of our patients between the fourth and seventh weeks. In their series, 17 patients showed conduction defects between the fifth and thirteenth days of the diphtheria; in our one fatal case, in which the myocarditis developed on the thirty-eighth day, an A-V dissociation may have been present. Fourteen fatalities occurred in their series, one occurred in ours. In both series, neuritis was associated with myocarditis in high incidence. It would thus appear that the myocarditis which follows cutaneous diphtheria is essentially identical with that

which follows faucial diphtheria, but is a less frequent complication and one which develops at a later period after the onset of the infection.

Ball⁹ has described the evolution of RS-T segment and T-wave changes in two cases of myocarditis after faucial diphtheria. These patients showed no clinical evidence of heart disease. Burkhardt, Eggleston, and Smith⁸ consider the T-wave changes to be the result of intoxication rather than of structural

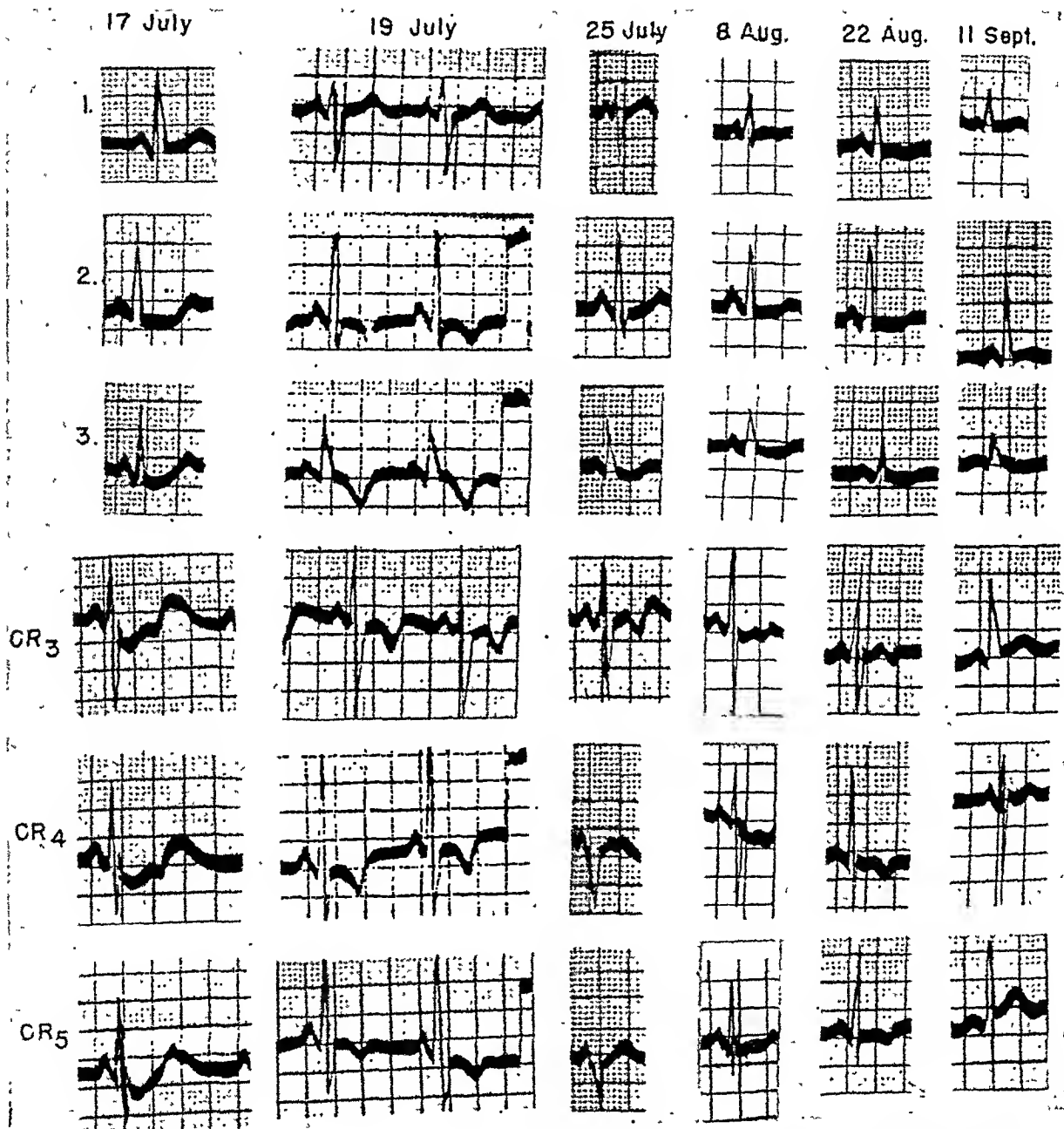


Fig. 5.—Definite myocarditis (after faucial diphtheria). Onset of faucial diphtheria June 15. Onset of severe neuritis about forty-eighth day. Antitoxin was not given. Cardiac symptoms consisting of severe substernal pain and dyspnea set in about the twenty-fifth day. The electrocardiograph showed a rate of 80 to 90, with a normal sinus rhythm. The P waves were large and peaked. The P-R interval was 0.14 to 0.17 second. The QRS complexes were widened and slurred, with a maximum interval of 0.11 second. The early tracings showed depression of the R-ST segment in all leads. The T waves were bizarre and changed rapidly. There was a progressive improvement in the tracing, which appeared relatively normal on September 11 (eighty-eighth day).

damage to the myocardium and consider them to have little or no prognostic value. We are not entirely in agreement with this opinion, in view of the clinical evidence of heart disease in three of our patients in whom the electrocardiographic changes were of the T-wave type. Our view that T-wave changes do have prognostic value is supported by an example of severe heart disease following faucial diphtheria. The symptoms and signs in this patient resembled those of a severe coronary occlusion. The first tracings taken showed only marked RS-T segment and T-wave abnormalities, but intraventricular conduction defects developed a few days later (Fig. 5). We feel that the RS-T segment and T-wave abnormalities are the result of an early or mild myocardial involvement and are potential precursors of later, more serious involvement.

SUMMARY

1. The myocardial complications which developed in a group of 140 patients with cutaneous diphtheria have been considered.

2. Shortly after cutaneous diphtheria was first observed in this hospital we became impressed with the gravity of the myocardial complications, and measures were instituted in an effort to recognize this complication early and to prevent death from this cause. The measures adopted may have been more stringent than necessary.

3. Definite myocarditis appeared in four patients, one of whom died. The diagnosis was considered probable in three additional patients, an incidence of 5 per cent. In seven other patients the diagnosis could not be excluded entirely.

4. The symptoms, signs, laboratory studies, and electrocardiographic findings in these patients are discussed.

5. Cardiac complications developed from the fourth to seventh week after the onset of the skin lesions. Their duration was from one to three months. All patients who survived showed no evidence of cardiac abnormality after four and one-half months from the onset of the skin lesions. The electrocardiograph is an essential in the diagnosis and evaluation of the myocarditis.

6. A definite parallel relationship existed between the severity of the cutaneous lesions and development of cardiac complications. Of 18 patients with very severe cutaneous diphtheria, four (22 per cent) developed myocarditis; whereas the complication did not appear in any of the 50 patients in whom the cutaneous lesions were mild.

7. Neuritis developed as a complication in the three patients with definite myocarditis who survived, and in one of the three patients in whom the diagnosis of myocarditis was probable. The onset of neuritis either preceded, or coincided with, or followed the onset of the myocarditis.

8. It is concluded that myocarditis is an infrequent complication of cutaneous diphtheria, but one which must be especially considered in any patient in whom the degree of cutaneous involvement is severe.

The author is indebted to Colonel Francis C. Wood for his many helpful suggestions and to First Lieutenant Thelma Cline for invaluable technical assistance in the course of this study.

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THE PRESENCE AND PATHOGENESIS OF ENDOCARDIAL AND
SUBENDOCARDIAL DEGENERATION, MURAL THROMBI, AND
THROMBOSES OF THE THEBESIAN VEINS IN CARDIAC
FAILURE FROM CAUSES OTHER THAN
MYOCARDIAL INFARCTION

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FIBROSIS or fibrinoid changes of the endocardium, with or without a leucocytic infiltration, and hydropic degeneration of the subendocardial myocardium are commonly found in noninfarcted hearts of patients having signs and symptoms of congestive heart failure, regardless of the etiology of the failure. Much less commonly, in addition to the endocardial fibrosis and subendocardial hydropic degeneration, ventricular mural thrombi and thromboses of the thebesian veins may occur. In the following two case reports all of the aforementioned morphologic changes were present.

CASE REPORTS

CASE 1.—

Clinical History.—On Jan. 16, 1945, the patient, a 29-year-old white man, was admitted to the hospital complaining of hoarseness, pain on swallowing, and persistent cough. In March, 1943, he had a brief episode of hoarseness. The hoarseness recurred in June, 1944, and persisted. In December, 1944, he began to cough and lose weight. The physical examination revealed hoarseness and diffuse audible pulmonary râles. A laryngoscopic examination showed swelling, infiltration, and ulcerations of both false and true vocal cords. The complete blood count, sedimentation rate, and urinalysis were within normal limits. The Kahn test for syphilis was negative. The sputum was positive for acid-fast bacilli. An x-ray film of the chest revealed widely disseminated densities throughout both lung fields. Planigraphic films showed two small cavities in the left upper lobe.

The patient was put on bed rest and given a high-caloric, high-vitamin diet. He was uncooperative in the maintenance of bed rest and voice rest. His symptoms became progressively worse and there was progressive weight loss. He died with manifestations of circulatory failure on April 16, 1945.

Clinical Diagnosis.—Bilateral, pulmonary, tuberculosis, with cavitation in left upper lobe; and tuberculous laryngitis.

Necropsy Abstract.—The left lung weighed 1,050 grams and the right weighed 1,308 grams. Both lungs were heavy and firmly consolidated. In the left lung near the medial border in the upper lobe there were two cavities, each measuring 3 cm. in diameter. They contained thin reddish gray fluid. The walls were thin. On section, the cut surfaces of the lungs were everywhere studded with innumerable small white tubercles. These were fairly uniform in size, averaging about 4 mm. in diameter. Most were moderately hard and stood out from the cut surface. A few yellowish caseous areas were noted in the apices and in the hilar region. These areas measured 1 to 2 cm. in diameter. A few dense strands of grayish blue fibrous tissue were noted running through the lung in the same regions. A moderate amount of turbid grayish red fluid flowed from the cut surface.

The heart was slightly enlarged; its weight was 480 grams. There was distinct dilatation of the right side. The epicardium was smooth and intact and contained a moderate amount of pale yellow fat. The endocardium of the left auricle and ventricle was smooth and translucent. The foramen ovale was closed. The right auricle and ventricle were filled with a large soft currant-jelly clot. On removing this clot, numerous gray rounded mural thrombi were seen to almost completely line the right ventricle. These thrombi were firmly adherent to the endocardium. They were lodged between the trabeculae carneae, and their smooth, rounded surfaces projected slightly into the lumen of the chamber. A moderate number of similar thrombi, although smaller in size, were found in the right auricle. The valves were all normal. The aortic cusps were thin and accurately apposed at the commissures. The myocardium presented a normal pattern of fibers. It was pale gray red in color. The left and right ventricular walls measured 1.3 and 0.8 cm., respectively, in thickness. The increase in the size of the heart was mainly accounted for by the right ventricular hypertrophy. The coronary arteries presented clear lumina of good caliber in all main branches. Their intimal surfaces were smooth and white.

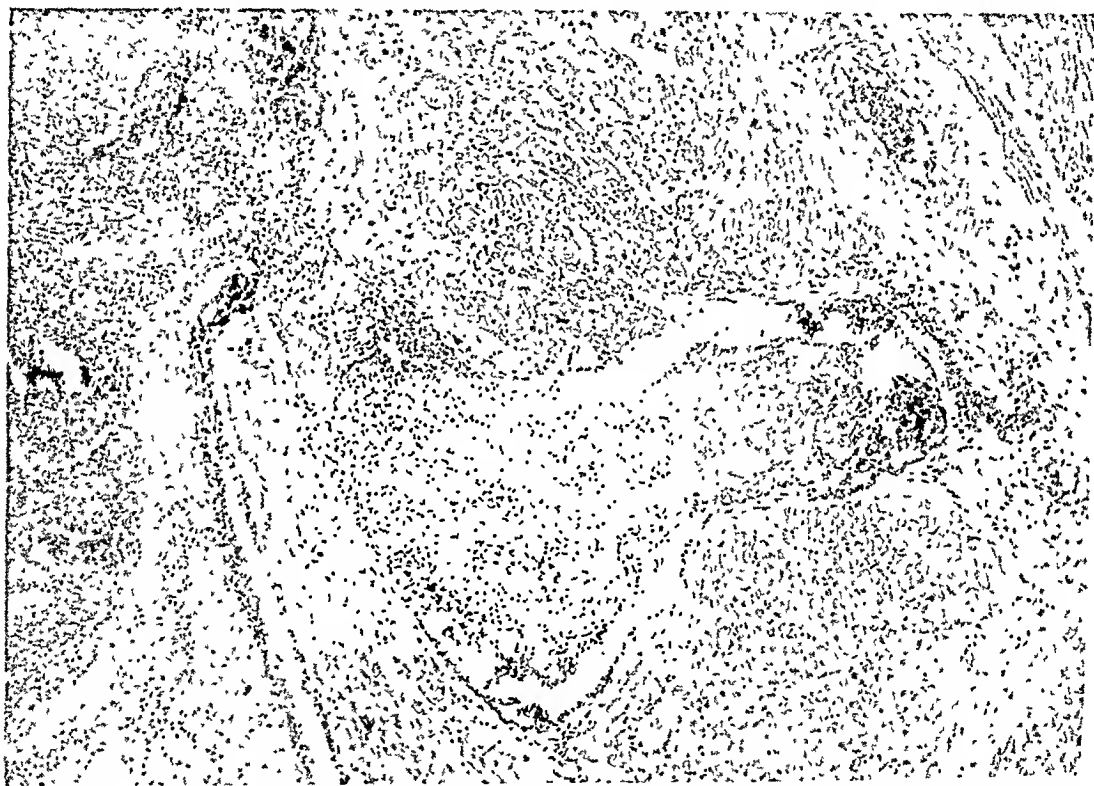


Fig. 1.—Case 1. Photograph of right ventricle showing the mural thrombosis in the interspaces of the trabeculae carneae and the thrombosis of a thebesian vein. ($\times 100$). (U. S. Army Medical Museum, Negative 89589.)

On the anterior wall in the upper portion of the esophagus there were irregular ulcerations measuring 2 to 4 mm. in diameter. The larynx showed marked ulcerations of both the true and false vocal cords. The mucosal surfaces were covered with irregular shallow ulcerations. Similar ulcerations were present on the posterior surface of the epiglottis.

Microscopically, the lesions of the lungs, epiglottis, and esophagus all showed the typical morphologic changes of tuberculosis. Acid-fast rods were easily demonstrated in the various lesions. No appreciable sclerosis of the pulmonary vessels was noted. The histologic sections through the right ventricle revealed the mural thrombi to be made up of areas of platelets mixed with polymorphonuclear leucocytes, alternating with areas of erythrocytes. A considerable proportion of the erythrocytes was well preserved. Thrombi of the same structure blocked and massively distended the thebesian veins. Some smaller

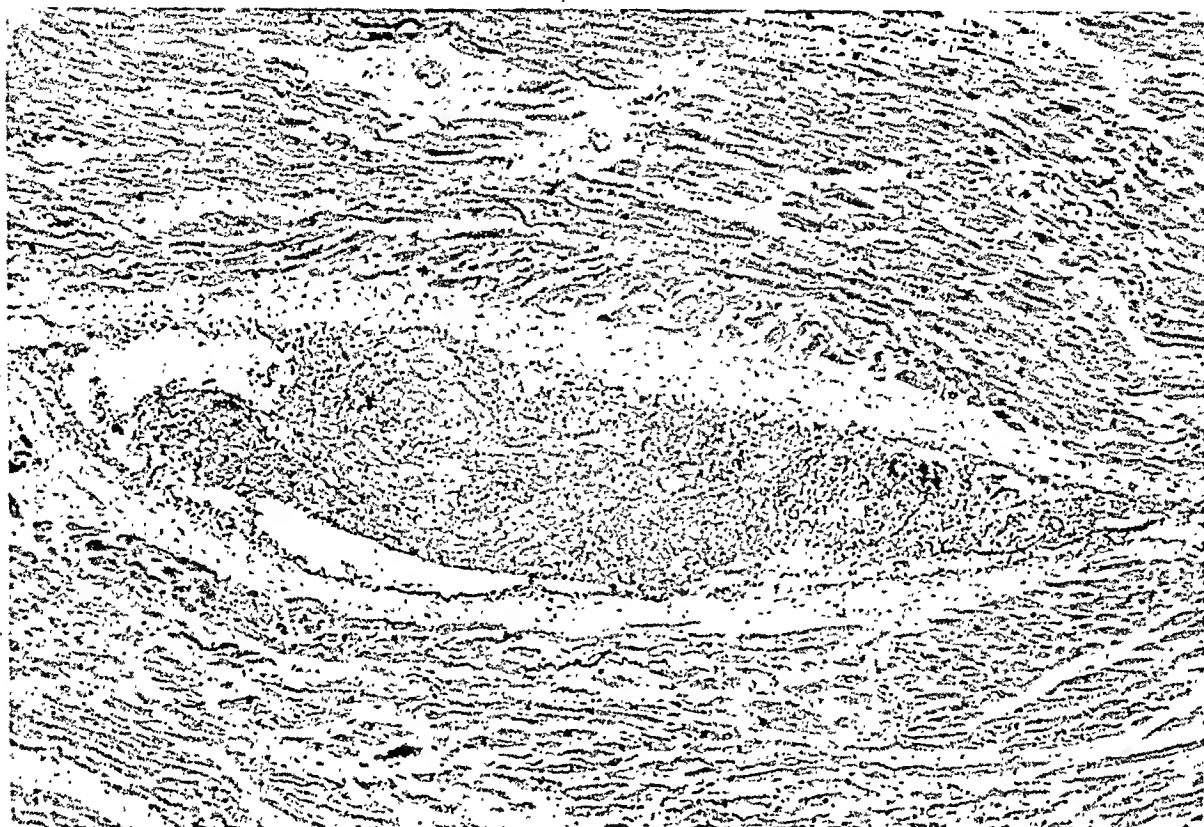


Fig. 2.—Case 1. Photomicrograph of right ventricular myocardium showing thrombosed thebesian vein. ($\times 100$.) (U. S. Army Medical Museum, Negative 89592.)

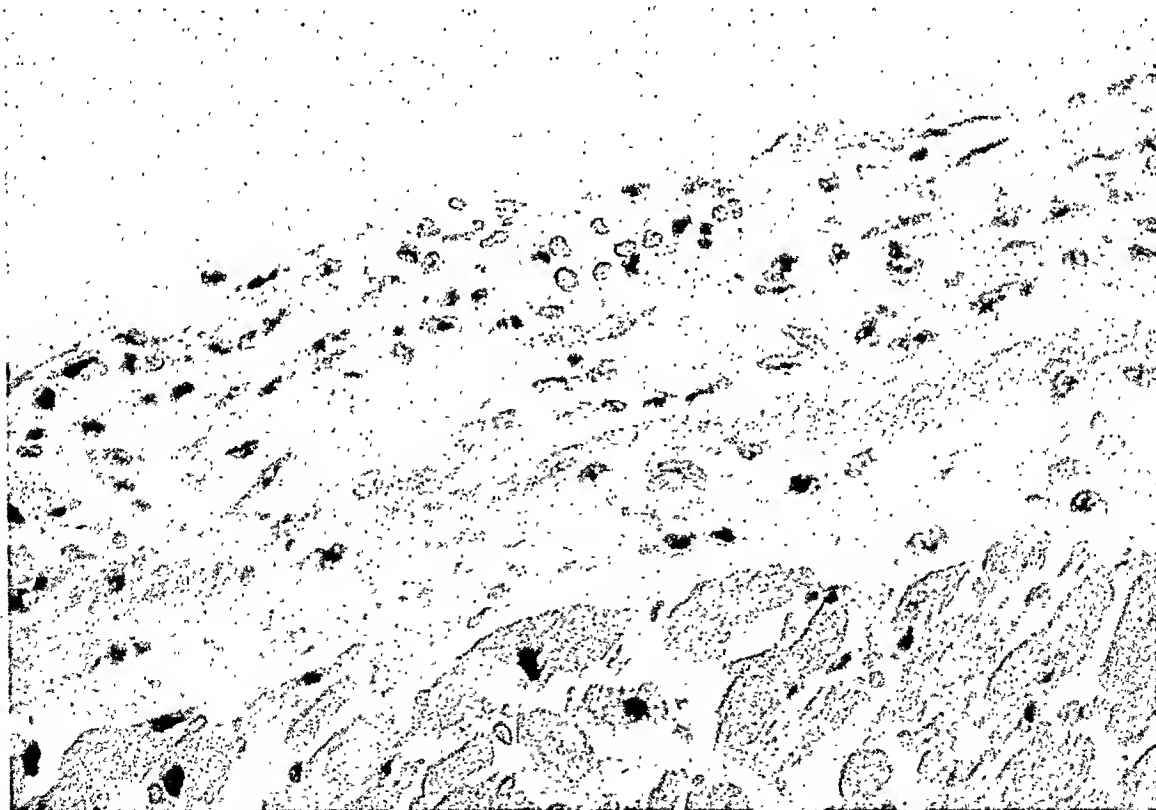


Fig. 3.—Case 1. Photomicrograph showing widening of the endocardium of the right ventricle, fibrinoid change of the connective tissue, and infiltration by polymorphonuclear leucocytes. ($\times 700$.) (U. S. Army Medical Museum, Negative 89590.)

thrombi were found in veins deep in the myocardium and even in the epicardium. In many places the endocardium itself was infiltrated with polymorphonuclear leucocytes. Under such an infiltrated area, a thin layer of subendocardial myocardium stained a deep pink, and showed pyknotic nuclei. Elsewhere some of the subendocardial muscle fibers were swollen and pale staining. There was a diffuse sprinkling of lymphocytes in many areas of the myocardium. These were accompanied by occasional polymorphonuclear leucocytes and large mononuclear cells. Small foci of these cells were occasionally seen beside blood vessels. The right auricle showed the same changes as the right ventricle. The left ventricle showed only slight swelling and vacuolization of the subendocardial muscle fibers.



Fig. 4.—Case 1. Photomicrograph showing two thrombosed thebesian veins of the right ventricle. ($\times 69$.) (U. S. Army Medical Museum, Negative 89591.)

Anatomic Diagnosis.—Bilateral pulmonary tuberculosis with cavitation of the left upper lobe; tuberculosis of the larynx and esophagus; degenerative changes in the endocardium of the right auricle and ventricle, with mural thrombi; thromboses of the thebesian veins of the right auricle and ventricle; hypertrophy and dilation of the right ventricle; bilateral lobular pneumonia.

Comment.—This case of rapidly progressive pulmonary tuberculosis was already far advanced when medical attention was sought. The patient's terminal signs were those of circulatory failure. At autopsy, tuberculosis was found to involve principally the lungs and larynx. The right side of the heart was dilated and lined with mural thrombi. There was fibrinoid degeneration and leucocytic infiltration of the endocardium in these chambers. The thebesian veins were dilated and freshly thrombosed. Since the pulmonary vessels were normal, the dilatation of the heart was presumably the result of a toxic effect of the infection on the myocardium.

CASE 2.—

Clinical History.—The patient, a 49-year-old white man, was admitted to the hospital on Sept. 27, 1943. He had been hospitalized fourteen times for congestive failure. His first hospitalization was in 1930, when he gradually developed edema, ascites, dyspnea, and palpitation. These symptoms were at first mild but gradually increased in severity. Previous to his first hospitalization he had been well except for gonorrhea in 1915 and recurrent attacks of tonsillitis, the last of which occurred in 1932. At the time of his first cardiac episode in 1930, after being hospitalized for sixteen weeks, he recovered sufficiently to return to military duty. In 1932, symptoms of cardiac decompensation recurred. This time he was given a medical discharge after fourteen years of service in the Army. Between 1932 and 1940 there were repeated episodes of heart failure, and hospitalization was required six times during this period.

On admission to the hospital in 1940, his chief complaints were dyspnea and orthopnea following an acute upper respiratory infection of seven days' duration. Physical examination revealed a blood pressure of 110/90 and evidence of pulmonary edema. There was a 2 plus albuminuria and a 2 plus pyuria. The blood nonprotein nitrogen was 30 mg. per 100 cubic centimeters. A diagnosis of "myocarditis with congestive heart failure" was made. The patient was treated with digitalis, rest, and diuretics. He was discharged as improved.

He was readmitted to the hospital in October, 1941, complaining of dyspnea, anorexia, cramps in the leg muscles, vertigo, and syncope. The blood pressure was 102/88. The heart was not enlarged. No cardiac murmurs or disturbances in the heartbeat were present. Gastrointestinal roentgenographic studies were normal. There was a 1 plus albuminuria. The diagnoses of generalized arteriosclerosis and mild cardiac decompensation were made. He was treated for congestive heart failure, from which he again recovered. He was readmitted to the hospital on Dec. 30, 1941, because of shortness of breath, edema of lower abdomen and legs, dysuria, and epigastric distress. There were no chest pains. Physical examination revealed distended neck veins, evidence of pulmonary congestion, and slight enlargement of the liver. The heart was enlarged, maximum intensity of the apex heartbeat being in the sixth intercostal space in the anterior axillary line. The pulmonary second sound was accentuated. There was moderate arteriosclerosis; the blood pressure was 120/90. In spite of the fact that typical murmurs were not heard and in spite of the fact that an x-ray film of the chest was not confirmatory, a diagnosis of mitral stenosis was made. The complete diagnosis on discharge was mitral stenosis and relative mitral insufficiency, generalized arteriosclerosis, hypertrophy of left ventricle, first degree auriculoventricular block, myocardial degeneration, and myocardial insufficiency.

The twelfth hospital admission for congestive heart failure took place on Oct. 10, 1942. One examiner reported the following: "This patient is a classical mitral stenosis type with right-sided failure, which goes into decompensation repeatedly." The maximum intensity of the apex beat was reported in the sixth intercostal space at the anterior axillary line. The heart sounds were diminished in intensity. The pulmonary second sound was accentuated. There was a rough, short presystolic murmur in the mitral area, with the suggestion of a diastolic murmur at the base of the heart. The heart rate was 72 per minute and the rhythm was regular. An electrocardiogram showed P-R intervals of 0.22, 0.26, and 0.24 second. After digitalization and rest the symptoms of cardiac failure disappeared.

The patient was readmitted to the hospital for the thirteenth time on Dec. 9, 1942, because of the recurrence of congestive heart failure. Examination revealed enlargement of the liver, ankle edema, distention of neck veins, and arteriosclerosis of the peripheral vessels. The blood pressure was 120/70. The electrocardiogram showed persistent first-degree auriculoventricular block, intraventricular block, and T-wave changes indicating diffuse myocardial damage. A presystolic apical murmur, low-pitched and rumbling, and a high-pitched diastolic apical murmur were heard. Enlargement of the left ventricle and left auricle was present. The congestive heart failure responded to digitalis, rest; and diuretics.

The fourteenth and last admission took place in September, 1943. Physical examination showed the skin to be dry, cool, and slightly cyanotic. There was evidence of intrapulmonary

and of pleural fluid, moderate arteriosclerosis, absence of pulsation of the dorsalis pedis arteries of both feet, moderate bilateral varicosities, and moderate ankle edema. The blood pressure was 108/76. The heart was markedly enlarged to the left, with the maximum intensity of the apex beat in the sixth intercostal space at the anterior axillary line. There was an apical systolic murmur, soft and blowing. The neck veins were distended. Slight enlargement of the liver was noted. No ascites was present. On this admission albuminuria and moderate secondary anemia were present. The electrocardiogram revealed evidence of severe myocardial damage, first degree auriculoventricular block, and left axis deviation. An x-ray film of the chest showed left ventricular enlargement and pulmonary congestion. During this admission the patient ran the gamut of all phases of congestive heart failure, showing nearly every type of cardiac arrhythmia and heart block. He had difficulty in voiding and required catheterization. Hemoptysis and leucocytosis appeared during the final two days. He expired at 11:05 A.M., Nov. 19, 1943.

Clinical Diagnosis.—*Heart disease.* (A) Etiological: (a) rheumatic fever, quiescent; (b) moderate generalized arteriosclerosis. (B) Structural: mitral stenosis and insufficiency; hypertrophy and dilatation of left and right ventricles; myocardial degeneration and insufficiency; pulmonary infarction. (C) Physiologic: auricular fibrillation; auricular paroxysmal tachycardia; A-V and bundle branch block.

Necropsy Abstract.—The heart weighed 485 grams. All chambers showed moderate hypertrophy and marked dilatation. The right auricle was especially dilated and the great veins leading into it were distended with blood. On the anterior surface of the left ventricle was an irregular milky white plaque about 3 cm. in diameter. The epicardium was otherwise smooth and intact; it contained a moderate amount of fat. Adhering to the endocardial surfaces of both ventricles, especially between the trabeculae carneae, were numerous mural thrombi. Most of these were red and showed fine white layers on section. They measured up to 3 cm. in diameter. Some of the thrombi were grayish brown and showed slight central softening. Both of the auricular appendages were filled and distended with thrombi. The tricuspid valve measured 12.5 cm.; the pulmonic, 8 cm.; the mitral, 10 cm.; and the aortic, 7 centimeters. The tricuspid leaflets were thin, delicate, and translucent; the chordae tendineae attaching to them were thin and discrete. The pulmonic valves appeared normal except for distinct dilatation of the ring. The mitral leaflets were of normal configuration, thin, and delicate; their chordae tendineae were thin and showed no fusions. The aortic cusps were thin and accurately apposed at the commissures. The myocardium was brownish red with a striking yellowish gray cast, and of rather flabby consistency. The fibers were poorly defined. Scattered through the myocardium were tiny translucent gray areas measuring 1 mm. or less in diameter. These were located principally in the regions beneath the mural thrombi. In the region of the apex, the wall of the left ventricle was thinned, measuring in places no more than 5 millimeters. In this area strands of gray fibrous tissue were noted in the myocardium. The endocardium over these areas was thick, white, and fibrous. Elsewhere the left ventricular wall averaged 1.4 cm. in thickness, while the right ventricular wall averaged 0.4 centimeter. All principal branches of the coronary arteries were of large caliber; there were no occlusions. The walls of these vessels were elastic, and their intimal surfaces were white and perfectly smooth.

Microscopic sections through the mural thrombi showed striking degeneration and fibrosis of the endocardium and subendocardial myocardium beneath the thrombi. In the trabeculae carneae the muscle fibers were almost completely replaced by loose fibrous tissue containing considerable numbers of young fibroblasts. The outlines of groups of muscle fibers were represented here and there by fibrinoid material staining bright pink. The fibrous tissue was highly vascular and contained numerous large capillaries, which were for the most part congested. There were many ecchymoses. Numerous large and small mononuclears and pigment-filled mononuclear macrophages were scattered through the fibrous tissue. There were a few polymorphonuclear leucocytes. The mural thrombi were densely adherent to this degenerate endocardium and subendocardium. The endothelium was entirely destroyed. The capillaries and fibrous tissue grew from the endocardium into the thrombi at various points.



Fig. 5.—Case 2. Photomicrograph of right ventricular myocardium showing marked endocardial fibrosis and hydropic degeneration of the subendocardial myocardium. ($\times 130$.) (U. S. Army Medical Museum, Negative 87901.)



Fig. 6.—Case 2. Photomicrograph of left ventricle showing mural thrombus formation and endocardial fibrosis. In the subendocardial myocardium there is an inflammatory cell infiltration and extensive myomalacia with replacement fibrosis. The islands of surviving muscle fibers show marked hydropic degeneration. The identity of the thebesian veins is lost in the fibrotic tissue. ($\times 130$.) (U. S. Army Medical Museum, Negative 87904.)

The thrombi seemed to be of varying ages; some appeared to be fairly recent. Large groups of erythrocytes in various stages of preservation alternated with areas of fibrin and polymorphonuclear leucocytes. In the other portions of the thrombi dense strands of condensed fibrin threads staining bright pink were noted. Practically all of the trabeculae carneae were degenerated. In places other than the trabeculae carneae, the degeneration usually extended for variable distances below the endocardium. Organized thrombi within their lumina had converted the thebesian veins into solid cords of fibrous tissue. The coronary arteries appeared to be normal. The muscle fibers elsewhere in the myocardium were in some instances large and pale-staining. There appeared to be a distinct increase in the number of capillaries; many were congested. Sections through the auricles showed their endocardium practically covered with thrombi, the majority of which were rather recent. The subendocardial myocardium showed degenerative changes essentially similar to those in the ventricles except that the degeneration was present only in scattered areas and involved only a very thin layer of myocardium. Several of the larger myocardial veins contained thrombi, presumably the result of propagation from the thebesian veins. The remaining findings are listed in the anatomic diagnoses.

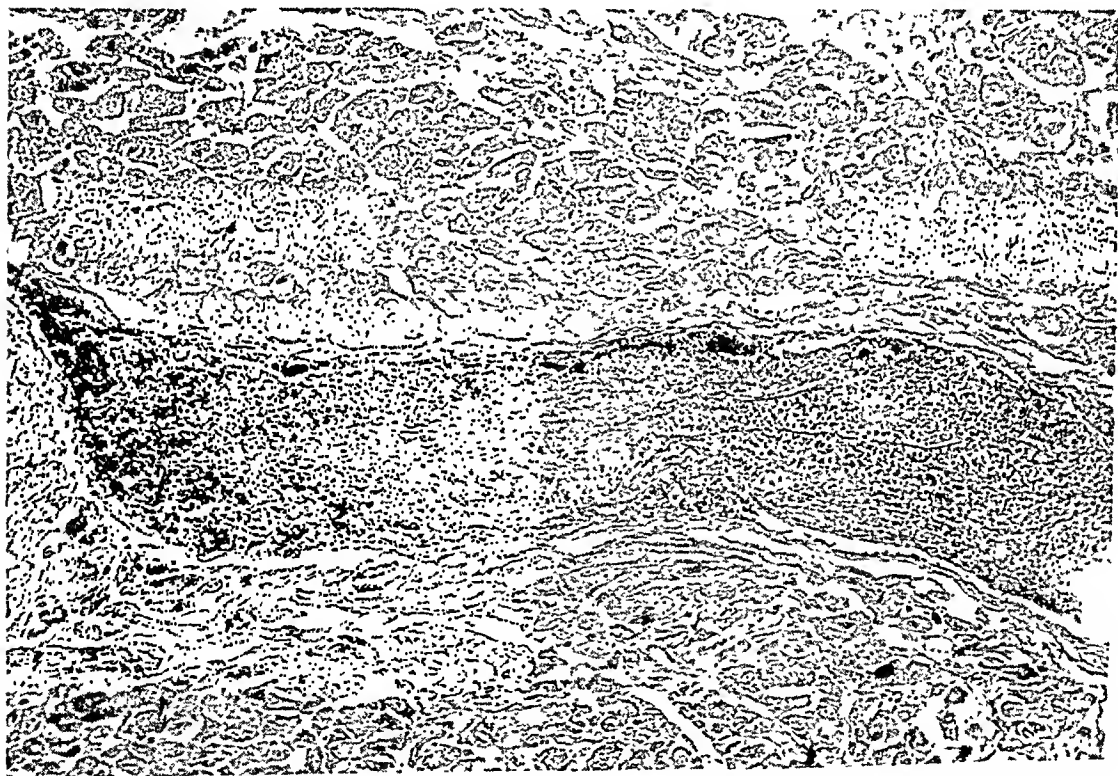


Fig. 7.—Case 2. A thrombosed venous sinus in the left ventricular myocardium. Note the hydropic degeneration of the myocardial fibers adjacent to one side of the vessel. ($\times 130$.) (U. S. Army Medical Museum, Negative 87902.)

Anatomic Diagnosis.—Degeneration and fibrosis of endocardium and subendocardial myocardium; mural thrombi in all cardiac chambers; organized thromboses of the thebesian veins and recent thromboses of larger myocardial veins; cardiac hypertrophy and dilatation; multiple bilateral pulmonary infarcts and infarcts of kidneys and spleen; congestion, necrosis, and fibrosis of the liver; fibrosis of the lungs; moderate generalized arteriosclerosis.

Comment.—This case was characterized by many bouts of cardiac failure necessitating fourteen hospitalizations over a period of thirteen years. At autopsy the heart weighed 485 grams. There was no evidence of rheumatic endo-

TABLE 1

CASE RACE SEX AGE (YR.)	CARDIAC PATHOLOGY	DURATION OF VENTRICULAR FAILURE	ETIOLOGY
A-41 White male 51	Weight 555 grams. Marked hypertrophy and dilatation of right and left ventricles. Slight to moderate coronary arteriosclerosis. Slight myocardial fibrosis. Slight subendocardial hydropic degeneration and fibrosis of the interventricular septum	2 weeks	Hypertensive heart disease
A-14 White male 42	Weight 470 grams. Slight right- and left-sided hypertrophy and dilatation. No appreciable coronary sclerosis. Rheumatic panmyocarditis. Myocardial fibrosis. Marked left ventricular subendocardial hydropic degeneration	1 month	Rheumatic heart disease
A-11 White male 50	Weight 470 grams. Dilatation and hypertrophy of right ventricle, dilatation of left ventricle. Marked coronary sclerosis. Myocardial fibrosis. Marked left ventricular subendocardial hydropic degeneration and marked fibrosis	1 year	Coronary sclerotic heart disease
A-12 White male 66	Weight 720 grams. Right- and left-sided hypertrophy and dilatation. Slight to moderate coronary sclerosis. Slight left ventricular myocardial fibrosis. Left ventricular subendocardial necrosis and fibrosis	2 years	Hypertensive heart disease
A-24 White male 70	Weight 560 grams. Marked left-sided hypertrophy and dilatation. Coronary arteriosclerosis. Left ventricular myocardial fibrosis. Extreme left ventricular subendocardial hydropic degeneration and necrosis. Thebesian vein thromboses, left ventricle. Mural thrombi, left ventricle	8 years	Coronary sclerotic heart disease
A-7 White male 46	Weight 750 grams. Hypertrophy and dilatation of all chambers. Marked coronary arteriosclerosis. No coronary occlusion. Left ventricular endocardial fibrosis. Slight hydropic degeneration of subendocardial myocardium of left ventricle. Mural thrombi left ventricle and right auricular appendage. Thromboses of thebesian veins, left ventricle	6 months	Hypertensive heart disease
A-34 White male 76	Weight 730 grams. Hypertrophy and dilatation of left ventricle. Subendocardial hydropic degeneration of left ventricle. Marked sclerosis of coronary vessels	3 years	Hypertensive heart disease, coronary sclerosis
A-29 White male 73	Weight 570 grams. Left ventricular hypertrophy and dilatation. Slight coronary arteriosclerosis. Fibrinoid necrosis of endocardium of left ventricle. Hydropic degeneration of subendocardial myocardium of left ventricle	6 days	Hypertensive heart disease

carditis, old or recent. All four chambers of the heart were lined by mural thrombi shading from red to gray. There was extensive endocardial fibrosis and subendocardial hydropic degeneration. The thebesian veins in these areas contained completely organized thrombi, making identification of the vessels difficult. No significant coronary arteriosclerosis was present. The heart valves were all normal. The etiology of the heart disease in this case is obscure. Similar cases have been ascribed, by Dock,¹ to beriberi. Smith and Furth² reported five cases in which there were cardiac hypertrophy and dilatation, and fibrosis of the endocardium and myocardium with mural thrombotic formation not attributable to arteriosclerosis, hypertension, or valvular heart disease. They raised the question as to whether the cardiac findings were associated with a deficient diet. In the case reported in this paper the patient was in comfortable economic circumstances during the latter part of his clinical course. At the onset of his illness he was in the Army, presumably eating at an Army mess.

TABULATED CASES

To determine the relative frequency of endocardial and subendocardial degeneration, mural thrombi, and thrombosis of the thebesian veins, eight autopsied cases of cardiac failure which were studied at necropsy were selected and the cardiac findings were tabulated. The criteria used in selecting these cases were clinical evidence of congestive failure and absence of anatomic evidence of myocardial infarction.

The etiology of the cardiac failure in the eight tabulated cases and the detailed case reports follow:

Hypertensive heart disease	4 cases
Rheumatic heart disease	1 case
Coronary arteriosclerotic heart disease	2 cases
Hypertension and coronary arteriosclerotic heart disease	1 case
Toxic myocardial disease	1 case
Beriberi (?)	1 case

Special stains indicated that the hydropic appearance is not related to glycogen deposition. In four of the cases fat stains showed the hydropic fibers to contain finely divided lipid.

DISCUSSION

It is to be noted that from an anatomic standpoint these 10 cases have in common the anatomic finding of cardiac dilatation and from a clinical standpoint evidence of ventricular failure. In all 10 hearts there was hydropic degeneration of the subendocardial myocardium of the dilated ventricle. In nine there was degeneration of the endocardium in the form of either fibrosis or fibrinoid necrosis. In four of these cases there were, in addition to the endocardial and subendocardial degeneration, extensive mural thrombi and thromboses of the thebesian veins. There were no instances of thromboses of the thebesian veins without mural thrombi or vice versa. The thromboses of the thebesian veins are undoubtedly secondary to the mural thrombus formation. It is suggested that the subendocardial fibrosis and subendocardial hydropic

degeneration are related to incomplete emptying of the dilated failing ventricle, with a resultant intraventricular stasis of blood having a reduced oxygen content. It has been established that a narrow zone of the ventricular and intraventricular subendocardial myocardium is nourished from blood contained within the ventricular cavities themselves. When mural thrombi are not present, the subendocardial hydropic degeneration is limited to the narrow zone usually spared in myocardial infarction.³ As a result of the circulatory stasis, oxygenation and nutrition of the subendocardial tissue are inadequate. The inadequate oxygenation and nutrition become manifest anatomically by hydropic degeneration and by necrosis and fibrosis of the tissue in this region. Such a sequence of events often leads to the formation of mural thrombi and to thrombosis of the thebesian veins in the involved areas.

The question of the clinical and physiological significance of these related phenomena may be justifiably raised although not conclusively answered by the data given here. In the second case report, a clinical and pathologic study yielded no adequate explanation of the repeated bouts of cardiac decompensation. It seems conceivable that following an initial episode of failure, caused perhaps by beriberi or some obscure toxic myocarditis, the heart may have been left functionally impaired, due to the morphologic changes described in this report. The correlation between the degree of anatomic valvular or peripheral vascular handicap of the heart and the severity of clinical heart disease is often not close. It is suggested therefore that these changes caused by intraventricular circulatory stasis in heart failure may predispose the heart to further episodes of decompensation.

SUMMARY

The cardiac pathology of 10 cases of heart disease which were characterized clinically by signs of myocardial insufficiency, and anatomically by ventricular dilatation, is given. Four of the patients had hypertensive heart disease; one, rheumatic heart disease; two, coronary arteriosclerotic heart disease; one, hypertension with coronary arteriosclerotic heart disease; one, a possible toxic myocarditis; and one, possible beriberi heart disease. In all 10 cases there was a hydropic degeneration of the subendocardial myocardium of the dilated ventricle. In nine of the cases there was degeneration of the endocardium, either in the form of endocardial fibrosis or fibrinoid necrosis with or without leucocytic infiltration. In four of these cases there was, in addition to the endocardial and subendocardial degeneration, extensive mural thrombi and thromboses of the thebesian veins. The suggested pathogenesis of the afore-mentioned alterations is intraventricular circulatory stasis, with inadequate oxygenation and nutrition of the portion of tissue normally supplied by blood in the ventricular cavity.

CONCLUSIONS

1. Endocardial and subendocardial myocardial degeneration are common morphologic alterations in patients dying of congestive heart failure.
2. Following subendocardial degeneration, mural thrombi and thromboses of the thebesian veins may occur. The thromboses of the thebesian veins are

secondary to the mural thrombi; the opposite is not true. These two findings are invariably associated.

3. These morphologic alterations can be explained on the basis of intra-ventricular circulatory stasis.

4. It is reasonable to expect that these morphologic changes further impair the function of the heart.

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Clinical Reports

VENTRICULAR FIBRILLATION

WITH SPECIAL REFERENCE TO THE MORGAGNI-ADAMS-STOKES SYNDROME;
REPORT OF AN UNUSUAL CASE

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NEWARK, N. J.

IN 1769 Morgagni first described a case of cardiac syncope with convulsive manifestations. This report was followed by similar reports by Adams in 1827 and by Stokes in 1846. Since these early reports, the slowness of the pulse has been the factor emphasized by most observers.¹ In fact, most textbook descriptions limit the term Morgagni-Adams-Stokes syndrome to those cases of syncope accompanied by slowness of the pulse. The Criteria of the New York Heart Association defines the Adams-Stokes syndrome as "that condition in which there are attacks characterized by unconsciousness, often accompanied by muscle twitchings, and even general convulsions. 'These attacks occur in patients with auriculoventricular block when the ventricular diastole is sufficiently prolonged to result in a severe grade of cerebral ischemia.' The duration and severity of an attack depend upon the length of the ventricular diastole."² The term is not applied to syncope due to other causes. However, in spite of this definition and its general acceptance, we feel that the concept of Parkinson, Papp, and Evans³ is more accurate since the original observers had no electrocardiographic studies by which to determine the true cause of the bradycardia and the resultant syncope. Certainly another mechanism, which we shall discuss as a causal factor of the syncopal attack, occurs with sufficient frequency to warrant its inclusion in the definition of the Morgagni-Adams-Stokes syndrome.

As a matter of fact, Parkinson and his co-workers,³ in a careful review of the literature up to 1941, found that of 64 cases in which electrocardiographic studies were made during the unconsciousness of the Adams-Stokes attack, almost one-half of the attacks were due to ventricular fibrillation and tachycardia and not to ventricular standstill alone. In view of these data, it is no longer compatible with fact to state that only instances of auriculoventricular or ventricular standstill be included in this syndrome. We feel, therefore, that the definition proposed by Parkinson, Papp, and Evans is much

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more applicable and should be generally accepted. They defined Stokes-Adams disease as "that condition which is seen in patients with heart block, who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these." It is important to bear in mind that in true Stokes-Adams disease, when there is ventricular standstill, the auricles continue to beat, whereas in other conditions of cardiac syncope there may be total cardiac asystole. Thus, this definition excludes cardiac syncope due to neurogenic or myogenic causes, such as vasovagal reflexes from stimulation of the carotid sinus, paroxysmal ventricular tachycardia complicating nodal bradycardia, and severe myocardial damage such as is seen in certain infections, all of which result in attacks of unconsciousness simulating Adams-Stokes disease. The absence of heart block and the episodic nature of the attacks readily distinguish them from the true Adams-Stokes syndrome.

Ventricular fibrillation, ventricular tachycardia, and ventricular standstill have usually been described in conjunction with the agonal phenomena of the dying heart.⁴ Only rarely have such arrhythmias been recorded in patients who have survived for any length of time. To date, only 28 such cases have been recorded, 13 of which showed ventricular tachycardia and ventricular fibrillation only, without cardiac standstill. The reason for such paucity of clinical material is obvious; ventricular fibrillation is usually fatal, so that a study of this arrhythmia in the living is extremely rare and therefore always worthy of careful observation and analysis. The mechanism for the production of ventricular fibrillation suggested by Wiggers⁵ is as follows: A premature systole appears during the vulnerable period of early diastole or late systole when certain elements of the cardiac syncytium have passed out of their refractory state. The impulse thus set up will weave its way through nonrefractory myocardial tissue to form a small wave front from which daughter excitation waves pass out over large portions of the myocardium. Then by the phenomenon of re-entry, smaller blocks of myocardium develop an independent excitation. The anoxia caused by incoordinated ventricular contractions causes failure of the coronary blood flow, which further slows conduction in the cardiac syncytium, decreasing fractionate contraction even more. This establishes the ventricular fibrillation.

Schwartz⁶ divided recurrent ventricular fibrillation into three stages. The first he designated as the prefibrillatory, the second as the fibrillatory, and the third as the postfibrillatory period. In the first stage there is an acceleration of the ventricular rate, with many extrasystoles of multifocal origin. The fibrillating stage shows a high rate of bizarre ventricular complexes appearing in irregular fashion. In the third stage there is a variable degree of ventricular standstill followed by ventricular tachycardia before the restoration of the basic ventricular rhythm. In this connection, it is worth mentioning that in 1937 Borg and Johnson⁷ reported a case of a 26-year-old man with syncope; they found that there was a stage of arrhythmia preceding unconsciousness, though no ventricular fibrillation occurred. In this patient the

prefibrillatory period was followed directly by ventricular standstill. This case serves to point out the facts that, although the three stages of Schwartz should be kept in mind, they are not absolute and that many cases do not conform to this classification, even though they are undisputed instances of Adams-Stokes disease. Moreover, the mere appearance of an arrhythmia prior to syncope does not necessarily mean that the syncope must be due to ventricular fibrillation, for it may also be caused by ventricular standstill alone.

In this brief discussion of the mechanism of ventricular fibrillation in Adams-Stokes disease, it will be of practical benefit to point out also the other conditions which may be instrumental in producing the syndrome. Cowan and Ritchie,⁸ in a review of 78 cases of complete heart block, found that only one-third showed the Adams-Stokes syndrome. Graybiel and White,⁹ in their report of 72 cases of complete heart block, showed that only 44 had bouts of Adams-Stokes disease. Therefore complete heart block is not the only factor essential to the production of the syndrome. Both Scherf,¹⁰ in the German literature, and Parkinson and his co-workers,³ in the English, divide the patients showing Adams-Stokes syndrome into three main groups. In the first group, the syncope is caused by ventricular tachycardia with resultant insufficient diastolic filling. The length of time before syncope will occur depends on the strength of the myocardium and the state of the arterioles at the time. In the second group, the symptoms are due to ventricular asystole which results from the failure of the ventricle to take over and establish its idioventricular rhythm. As we have previously mentioned, when this mechanism is active, it is difficult to determine by clinical method whether the asystole is of neurogenic or myogenic origin. In the third group, syncope is the result of a combination of ventricular tachycardia, with a subsequent period of ventricular asystole.

In most of the cases reported in the literature, the patients are among the older age group. This further emphasizes the fact that the state of the myocardium and the patency of the cerebral blood vessels play a definite and important role. As we have previously mentioned, the only recorded case in the younger age group is that of a 26-year-old man, reported by Borg and Johnson.⁷

We had the good fortune to observe a patient who suffered an attack of syncope produced by a combination of ventricular tachycardia, ventricular fibrillation, and ventricular standstill. We were able to record electrocardiographically the entire attack. Since only fifteen such cases are on record, this case has theoretical and clinical interest.

CASE REPORT

A. S., a 73-year-old white housewife, was admitted to the Newark Beth Israel Hospital, Dec. 11, 1943, following an attack of syncope. The past history was negative except that the patient had had two previous attacks of syncope. Five years before she had suffered her first attack when the door of a subway train closed upon her. Three years before our studies, the patient, who was an ardent horse race fan, suffered an attack of syncope as she was leaving the Belmont Race Track.

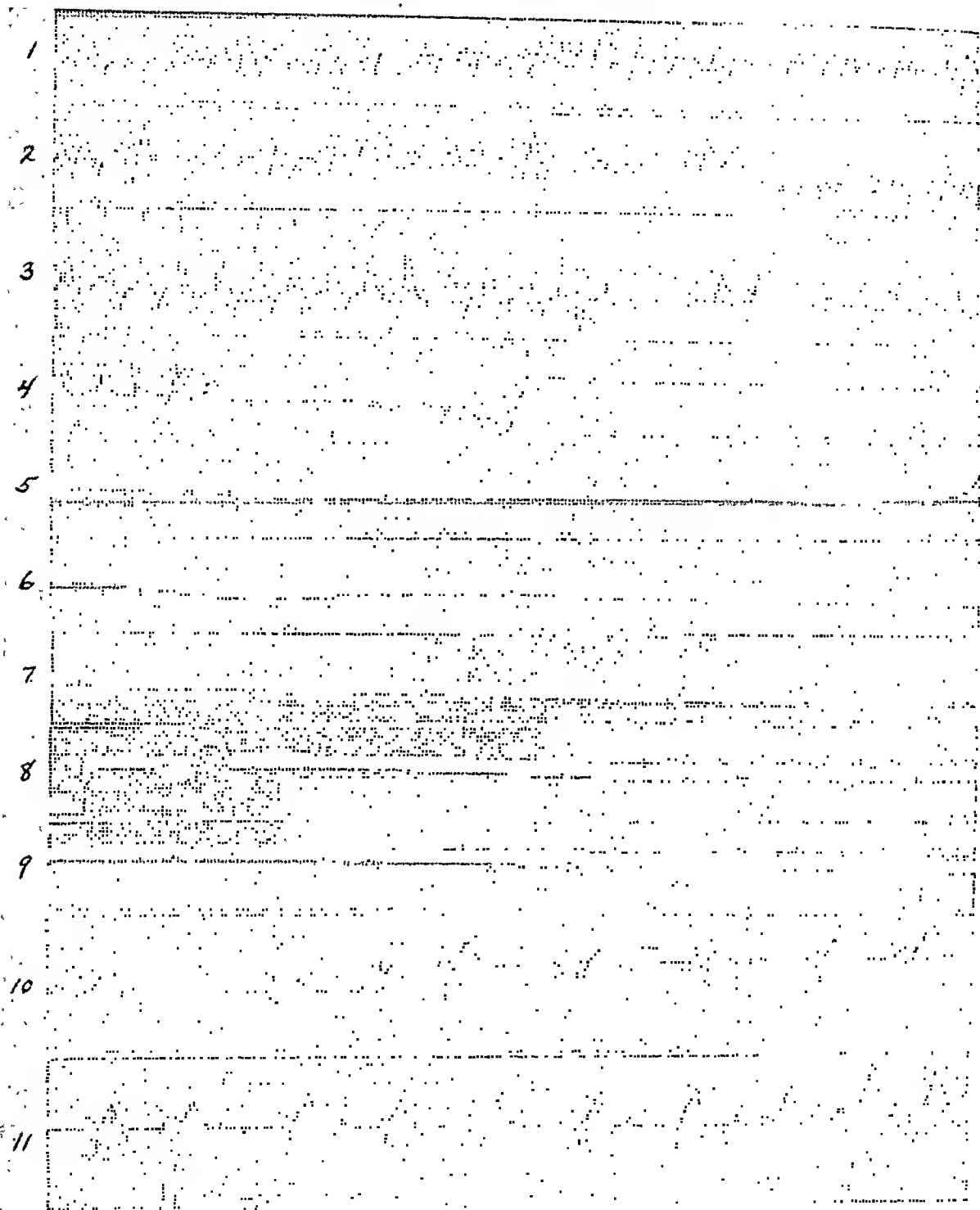


Fig. 14.

Figs. 1A, 1B, 1C, and 1D.—This is a continuous tracing, taken entirely on Lead III, during the patient's period of unconsciousness. Since it was started a few moments after the patient developed syncope, the presyncopal period is not recorded.

There is a period of ventricular fibrillation (Strips 1 and 2), followed by a short period of ventricular tachycardia (Strip 3). Ventricular standstill of 60.8 seconds is then seen (Strips 4 to 9). The auricles continue to function during the entire ventricular standstill at the rate of 32 beats per minute. A few idioventricular beats then occur, followed by ventricular beats from various foci (Strips 10 and 11). A period of pseudobigeminy, as a result of bidirectional complexes, is then seen, followed by so-called "chaotic heart action," in which multiple ventricular foci produce idioventricular beats of varied contour (Strips 12 to 22). This arrhythmia continues until the basic complete heart block appears for a short time (Strip 23). Then ventricular tachycardia interspersed with heart block recurs (Strips 24 and 25). Finally, the heart block is re-established as the dominant rhythm (Fig. 1D).

Her present illness dates back to Dec. 11, 1944, when the patient was found unconscious, in the street, in front of the office of one of the authors. She was in a completely unconscious state. Her face was cyanotic and flushed, and the pulse and heart sounds were unobtainable. No localized neurological signs could be elicited on cursory examination.

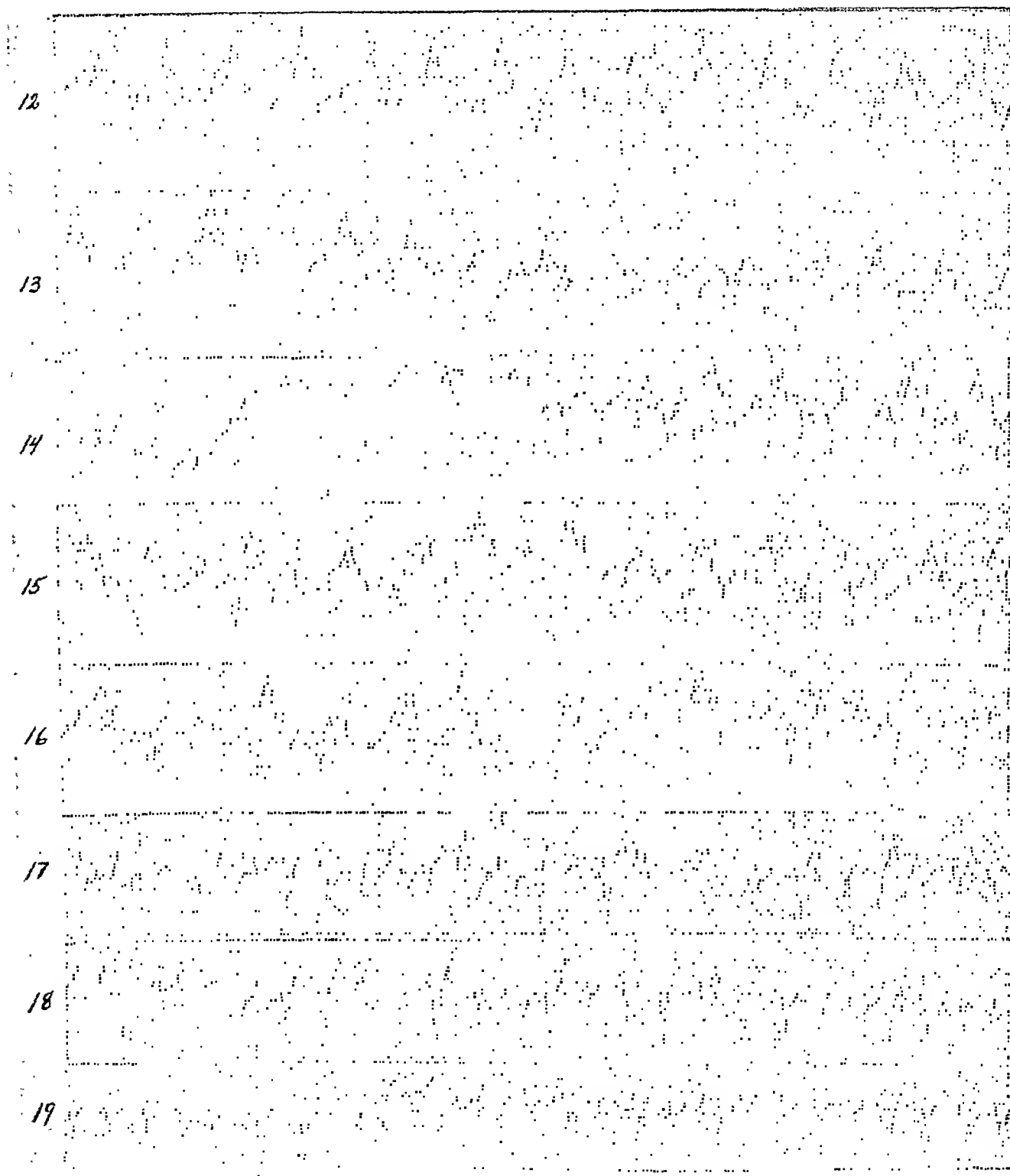


Fig. 1B.—(For legend see Fig. 1A.)

After several minutes, the patient vomited several times and developed clonic muscular twitchings involving both upper and lower extremities. During the ambulance ride to the hospital, she regained consciousness. Upon arrival at the hospital, her mind partially cleared, but she was thoroughly disoriented as to time and place and rambled vociferously.

10

21

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23

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Fig. 1C.—(For legend see Fig. 1A.)

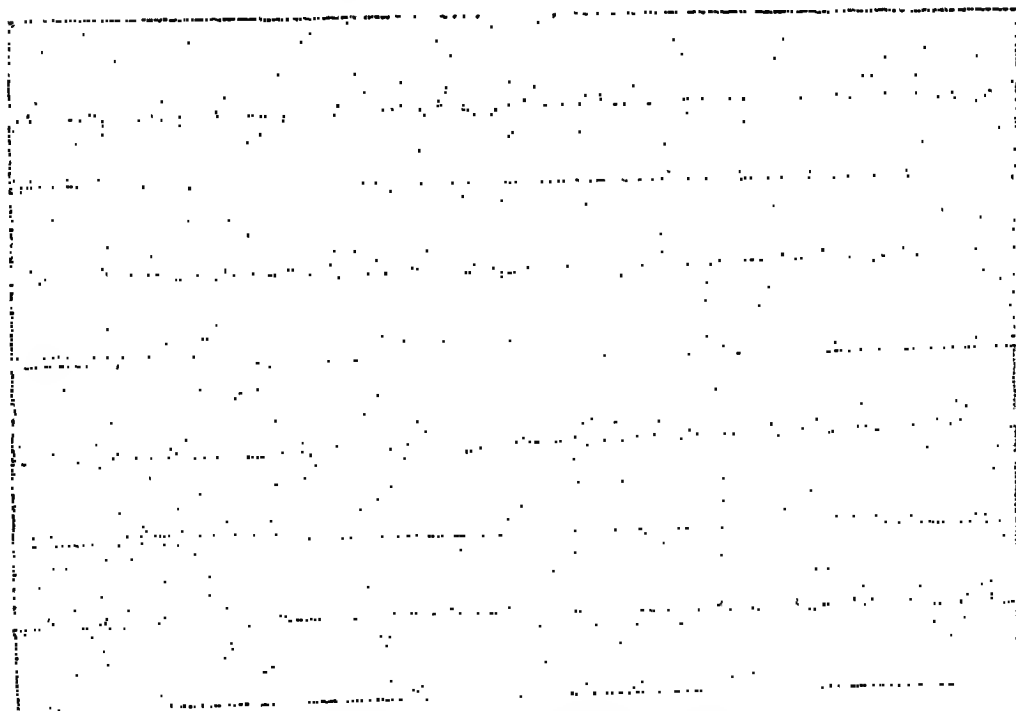


Fig. 1D.—(For legend see Fig. 1A.)

Physical examination revealed that the patient looked her stated 73 years of age. She could lie flat in bed. She was pale, rather than cyanotic. The pupils were equal and reacted to light and accommodation. The external ocular muscles were normal, the fundi showed an increased silver wire effect with prominent A-V nicking, the discs were negative, and there were no hemorrhages or exudates. The examination of the nose and ears was negative. The mouth was moist and clean. The pharynx was negative; the tonsils were small and imbedded. The neck veins were not distended. There was no lymphadenopathy and no thyroid enlargement. The chest was clear. The point of maximum impulse was located in the fifth intercostal space outside of the midclavicular line. The heart sounds were of good quality; a third heart sound, heard between two normal beats, was interpreted as being due to auricular beats. A_2 was greater than P_2 . There was a loud, harsh, long systolic murmur at the apex, transmitted to the anterior axillary line; another systolic murmur, somewhat softer, was heard at the aortic area. The pulse rate and ventricular rate were 42 per minute. The blood pressure was 180/60. The liver, kidneys, and spleen were not felt; there was no tenderness nor rigidity, and no palpable masses in the abdomen. The examination of the extremities showed marked Heberden's nodes, but no cyanosis, edema or clubbing; peripheral sclerosis was present. On neurological examination, the deep reflexes were equal and active; no pathologic reflexes were elicited.

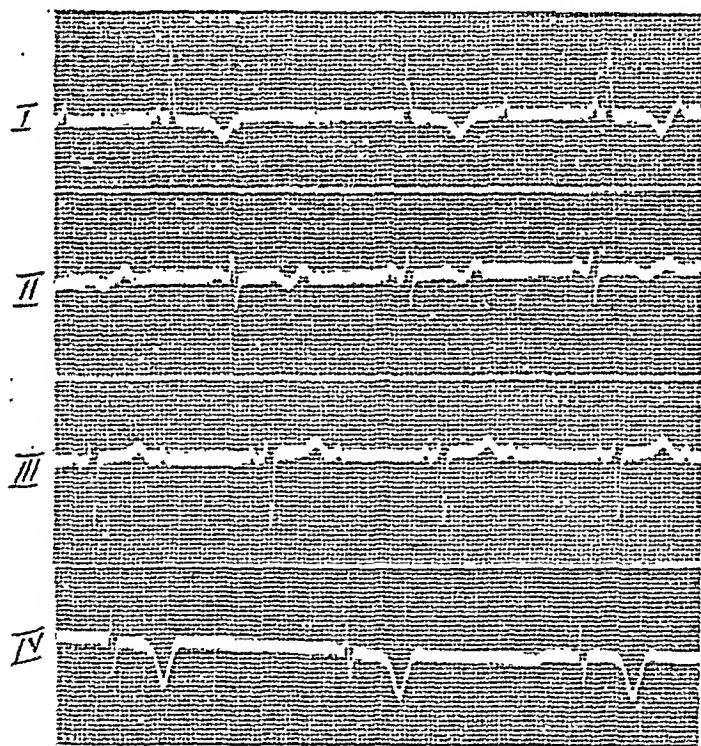


Fig. 2.—Tracing taken the day following, when the patient was apparently in her normal state. The rhythm is a two-to-one heart block with a nodal escape beat seen in Lead I. The abnormalities noted are inverted T waves in Leads I, II, and IV, with left axis deviation.

The clinical diagnosis was arteriosclerosis and hypertension, enlarged heart, mitral insufficiency, dilated aorta with complete A-V heart block, and Adams-Stokes syndrome.

The patient was placed on phenobarbital, $\frac{1}{2}$ grain four times daily, and papaverine, $1\frac{1}{2}$ grains three times daily. She remained much quieter and had no convulsive or syncopeal episodes.

On Dec. 12, 1943, she was taken to the electrocardiographic department. When the electrodes were applied, she suddenly turned a cadaveric white, the respiration ceased, the heart sounds became inaudible and the pulse imperceptible. The patient made a few gasping respiratory movements, and the pupils dilated. During this time, sphincter control ceased and she became incontinent of urine and feces. A continuous tracing of the events in the heart, during this whole episode will be found in the accompanying electrocardio-

grams (Fig. 1). Soon the face of the patient became suffused and cyanotic, there were some deep, sporadic respiratory movements, and the patient gradually returned to consciousness. During the ensuing three days the patient had several further seizures, each following the same general pattern. Fig. 2 illustrates the rhythm on the third day when the pulse was 40 per minute. After these episodes, she remained free from attacks, and her mind returned to normal. On the seventh day she refused to stay in bed and insisted on going home. She was discharged at her own risk.

Following these episodes, the patient has consistently refused medical care of any kind. She is perfectly rational, does her own housework, and will not permit further electrocardiographic studies to be made. Eighteen months have now passed since the first tracing was taken, and the patient has returned to full activity. Recently she was observed lifting bundles of paper averaging more than 20 pounds each.

DISCUSSION

A number of investigators have recorded cases of ventricular fibrillation, both in Adams-Stokes disease and in the dying heart. These reports emphasize the fact that ventricular fibrillation is rarely seen in the Adams-Stokes syndrome, unless the basic rhythm is some degree of heart block. Furthermore, the time when ventricular fibrillation is most apt to occur, is during the transition from partial to complete A-V heart block. However, this is not an inflexible rule, since cases have been recorded in which a patient with partial heart block has developed ventricular fibrillation without ever having reached a stage of complete auriculoventricular dissociation.

Instances of Adams-Stokes disease, which occurred during acute myocardial infarction following coronary occlusion, have been reported. Beckwith¹¹ recorded three such cases which demonstrated different underlying mechanisms. Complete heart block was present in one case and paroxysmal ventricular tachycardia in another; both conditions were present in the third. In none of the three patients were the syncopal attacks registered electrocardiographically.

Experimental ventricular fibrillation may be induced by ligation of one of the coronary arteries; it is therefore felt that this arrhythmia may be responsible for sudden death in acute myocardial infarction in the human subject. It is believed that afferent impulses from the infarcted area give rise to reflex coronary spasm by way of the vagi. This results in myocardial anoxia which may initiate the premature contractions that lead to fibrillation. It is interesting that Smith, McEachern, and Hall¹² found that the mortality rate from sudden occlusion of the left coronary artery in normal dogs could be reduced from 75 per cent to 50 per cent by the administration of quinidine. Death in these animals was usually due to ventricular tachycardia, followed by ventricular fibrillation. Quinidine seemed to prevent much of the pain of the occlusion. It is interesting to note that when quinidine was used instances of ventricular tachycardia and extrasystoles were more frequent, though there were fewer cases of ventricular fibrillation.

The prognosis, at best, is uncertain. Such patients usually have had advanced arteriosclerotic heart disease with marked coronary arteriosclerosis and myocardial fibrosis, and rarely survive more than a few months after an

attack. Our case is unique in that the patient is still active eighteen months after the recorded seizure and probably five or six years following the initial attack.

It may be pertinent to discuss the various forms of treatment suggested for this condition. Many years ago barium chloride was recommended as the drug most likely to prevent Adams-Stokes syncope. However, Parsonnet and Hyman,¹³ in a carefully controlled experimental study concluded that this drug was of no value. The use of adrenalin or ephedrine has been proposed because these drugs are such powerful cardiac stimulants; unfortunately, their true value in the therapy of this condition is not very clear. There is some evidence to show that in chloroform anesthesia the administration of adrenalin may, in itself, induce ventricular fibrillation.¹⁴ Ephedrine, too, because of its irritating effect on the myocardium, may be a dangerous drug in spite of the fact that theoretically it should prevent ventricular standstill. Quinidine sulfate has been used prophylactically in an attempt to prevent some of the arrhythmias, especially the extrasystolic ones, and thus forestall ventricular fibrillation. The experiments on dogs by Smith and his collaborators¹² are especially suggestive. However, quinidine, in excess, produces ventricular fibrillation in the experimental animal. More recently, Katz¹⁵ suggested the use of papaverine in large doses. Experimentally, at least, this drug has been found effective in both stopping and preventing ventricular fibrillation. From the previous consideration, it is evident that of the drugs suggested, the ideal one for the treatment of Adams-Stokes disease, or the component arrhythmias that produce it, has not yet been found. Until a better drug is found, therefore, papaverine in large doses, or perhaps quinidine, is the remedy of choice.

The report of this case helps to summarize the known facts on the Morgagni-Adams-Stokes syndrome, as well as on ventricular fibrillation. The patient was a woman, 73 years of age, when first seen. However, the condition must have been present for at least five years, in view of a clear-cut history of syncopal attacks five and three years prior to hospital admission. The observed attack did not demonstrate very clearly the three stages suggested by Schwartz; we were unable to record the so-called prefibrillatory period in our tracings. However, this stage may have been of such short duration that it was not observed before the onset of syncope. On the other hand, that the syncopal period followed the rather typical course pointed out by Parkinson is clearly demonstrated in the tracings. Ventricular fibrillation with a rapid rate was followed by a period of rapid ventricular tachycardia which was followed by another short period of ventricular fibrillation and, finally, by ventricular asystole. The auricles continued to beat during the entire period of ventricular asystole which, in this particular seizure, lasted for one full minute. The longest period of asystole thus far recorded is seventy-nine seconds.¹⁶ In our case, the asystolic period was followed by ventricular tachycardia with idioventricular beats and multifocal extrasystoles. Finally, a run of ectopic beats with bidirectional complexes appeared, and the heart rate slowed enough so that, when consciousness returned, the rhythm reverted to the heart block, which was originally present.

In the treatment of the condition, the only drug used was papaverine in large doses. It is difficult to say whether or not this contributed to our patient's recovery, since she recovered from her previous attacks without medication. During the past eighteen months she has taken no medication and apparently has had no further seizures.

It is important from a prognostic point of view to discuss the question of longevity in such cases. In the series of 56 patients reported by Parkinson and his co-workers, there were 15 with ventricular standstill alone. Five of these died during the attack and seven lived and were free from seizures for from three months to four and one-half years after the onset of Adams-Stokes disease. The remaining three of the series died of noncardiac causes. Of 20 cases similar to our own, 15 patients died during the attack and five died within a year after discharge. Only four of this group were alive after three to ten months.

Based upon the previous data, the prognosis in cases with very rapid ventricular tachycardia and fibrillation is immediately grave. However, if the patient recovers from the initial syncopal seizure, the life expectancy is about one year. Our patient has survived for 18 months after the one attack which was graphically recorded, and has probably lived now for six years since her first syncopal seizure which we assume to have been similar in character to the attack which we recorded.

SUMMARY

1. We have discussed the definition of the condition known as Adams-Stokes disease, or the Morgagni-Adams-Stokes syndrome. Based upon the review of the literature, we feel that the Adams-Stokes syndrome should include not only cases of ventricular standstill with loss of consciousness, but also those of syncope due to ventricular tachycardia or ventricular fibrillation.

2. An instance of this condition is reported which is unusual in that the patient lived six years, which is much longer than most patients live after the onset of syncope.

3. The varied methods of treatment are briefly summarized and found to be inadequate. At the present time, quinidine and papaverine seem to be the drugs of choice.

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ADDENDUM

April 15, 1946: This patient is still alive and able to carry on her daily routine as a housewife, two years and four months after the recorded attack. She refuses, however, to permit further study.

FATAL CORONARY FAILURE WITHOUT INFARCTION: REPORT OF A CASE

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FOR many years it has been taught that coronary artery disease primarily affects patients in middle life, but that it may occur infrequently in younger people. It has become apparent, however, that the incidence of coronary artery disease in young people is greater than is generally realized. It is possible that in many cases of coronary artery disease in young people where certain significant symptoms are present, the physician may be misguided in his diagnosis or may be lulled into a false sense of security solely because of the youth of the patient. In many cases severe disability or even fatality may result.

REPORT OF CASE

History.—A 25-year-old white man was admitted to the Station Hospital at 10:45 A.M., on Feb. 7, 1945, in a semicomatose state. He was disoriented, cyanotic, and apparently in moderate shock. Approximately two hours after admission, when he was able to speak, he stated that he was well until one-half hour before admission, when he felt a pain around his heart, associated with some shortness of breath. These symptoms became progressively more severe, until he felt that he had to lie down. The last thing he remembers was stretching out on the ground outside the building in which he was working. Within a few minutes he was found, unconscious, by several of his fellow workers. He was bleeding from the nose and showed marked blueness of the hands and face. His pulse was said to be imperceptible. The breathing was described as very shallow, quickly becoming very irregular and weak. The blueness of the face and hands increased. After the administration of artificial respiration breathing improved considerably and the patient was brought to the hospital.

The history revealed that the patient had been a mechanic in civilian life, and was inducted into the Service in February, 1942. He smoked cigarettes moderately, drank a large amount of beer, and occasionally went on an alcoholic bout. He did not take any drugs. His father, mother, and one sister were living and well. An uncle on the paternal side had died of a heart attack at the age of 40 years. There was no other history of chronic or familial disease. He had had the usual childhood diseases, but no other illnesses except infrequent upper respiratory infections. He denied any venereal disease. He also stated that beginning approximately one month prior to this episode of fainting he noticed pain in the chest, localized under the breastbone, which occurred only following or during exertion, such as walking, physical training, or heavy lifting. He described the pain as a cramping sensation similar to muscle cramps. There was no radiation and the pain was definitely relieved by rest. He could not recall experiencing any attacks of pain while at rest. Although for two weeks prior to admission to the hospital, he was unable to keep up with his physical training periods because of the quick onset of this cramping sensation, he did not seek medical advice. He also stated that he had felt vague pains through his arms and legs during the month preceding admission. These pains were not related to the chest pain or to activity.

Physical Examination.—On admission the patient was disoriented, confused, and very anxious. He was stocky and heavyset. His height was 71 inches, and his weight was 180 pounds. His skin was cold and clammy; there was moderate cyanosis of the lips, face, and nail beds. The pupils were widely dilated and reacted sluggishly to light. There was evidence of fresh bleeding from the nose. The mouth and throat were normal. There was

no neck rigidity and no enlargement of the cervical nodes or of the thyroid. The lungs were essentially normal. The heart was not enlarged; the rhythm was regular and the rate was 74 beats per minute. The sounds were of good quality and no murmurs nor friction rub were heard. The blood pressure was 130/78. The abdomen was normal. There was incontinence of feces. The musculoskeletal system was essentially normal, and all reflexes were present and equal, bilaterally. There was no impairment of any of the cranial nerves.

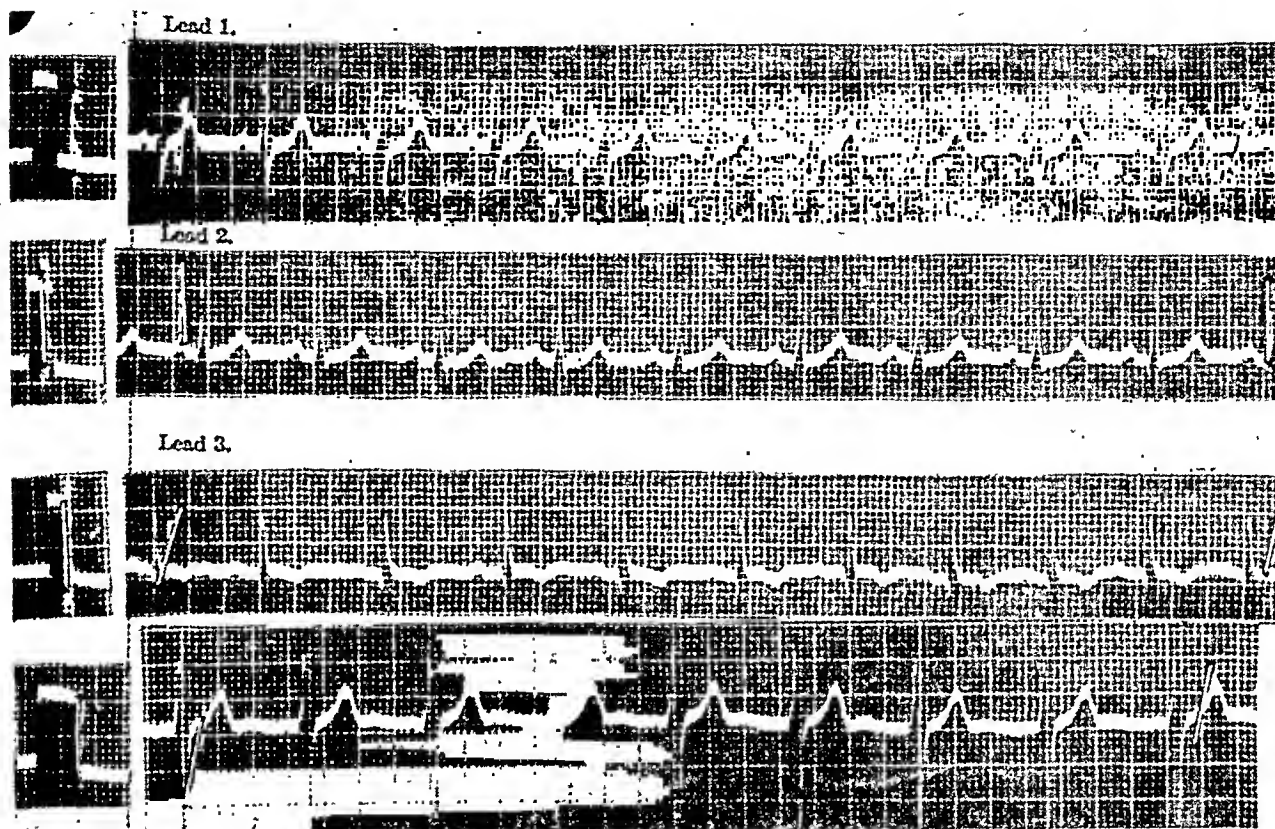


Fig. 1.—Electrocardiogram taken four hours after first episode of syncope.

Course.—Within two hours after the acute episode, the patient was feeling much better but still complained of a slight pain in the chest, substernally. The temperature, pulse, and respirations were all normal. The skin was warm, there was no evidence of cyanosis, and the patient was well oriented and rational. An electrocardiogram (Fig. 1) taken at this time revealed a regular sinus rhythm, a rate of 88 beats per minute, a deep S_1 , and inversion of T_1 . The electrocardiogram was interpreted as being within normal limits. The patient was kept on absolute bed rest and given phenobarbital, $1\frac{1}{2}$ grains, at bedtime. On Feb. 8, 1945, the day following the acute episode, he complained of a persistent, mild substernal pain. This symptom recurred on several occasions during the following weeks. It was noted at this time that the patient had a rather large conjunctival hemorrhage in the right eye. The external ocular muscles, vision, and fundi were found to be normal. The blood pressure was 146/78. All reflexes were present and equal. There was no evidence of any neurological pathology and no derangement of the cranial nerves. The patient remained on complete bed rest from Feb. 7, 1945, until Feb. 20, 1945. During this period the temperature remained consistently normal. The white blood count, taken on Feb. 8, 1945, revealed 8,200 white blood cells, with 52 per cent polymorphonuclears, 44 per cent lymphocytes, 2 eosinophiles, and 2 monocytes. The sedimentation rate was 7 mm. in one hour. On Feb. 13, 1945, the test revealed 7,400 white blood cells, with 50 per cent polymorphonuclears, 48 per cent lymphocytes, and two eosinophiles. The sedimentation rate was 6 mm. in one hour. The Kahn test for syphilis was negative. The electrocardiogram taken Feb. 12, 1945 (Fig. 2), was interpreted as being within normal limits. In the absence of physical or laboratory findings of myocardial injury, the patient was allowed to

increase his activity gradually, and to get out of bed on Feb. 21, 1945. On Feb. 25, 1945, he was given a two-hour pass to visit his barracks. He returned within a short time, stating that he had had to stop and rest three times in a distance of approximately two blocks because of precordial pain. The patient was again put on bed rest. At 7 A.M., on March 4, while still in bed, he complained of severe substernal pain, and in a few minutes went into acute circulatory collapse. He was given oxygen and $\frac{1}{4}$ grain of morphine, intravenously, but did not improve. He developed a gallop rhythm and expired thirty minutes after the onset of the precordial pain.

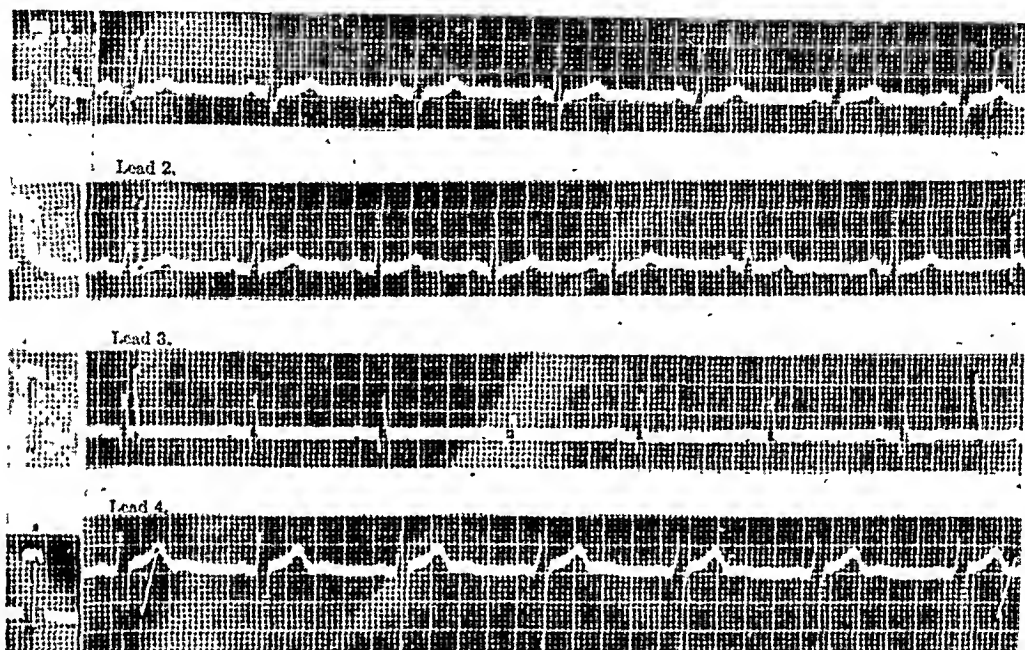


Fig. 2.—Electrocardiogram taken Feb. 12, 1945.

Necropsy.—Post-mortem examination revealed that the abnormal findings were confined entirely to the heart and aorta. A considerable fatty layer over the pericardial sac was cut through and the heart was exposed. There was a normal amount of clear yellowish fluid within the pericardial sac. The heart appeared to be of normal size, and weighed 380 grams. The right ventricle was relaxed and flabby; the left ventricle was firm and moderately contracted. The epicardium was smooth. The relationship between the musculature of the right and left ventricles was normal. Upon opening the heart several small clots which were not adherent to the endocardium were observed in the left ventricular chamber. The endocardium throughout both ventricles appeared smooth and glistening. The papillary muscles were normal. There was no evidence of old or recent myocardial scar formations. All the valves were found to be smooth and free. In the first portion of the ascending aorta a moderate amount of soft, atheromatous plaque formation was present on the wall of the vessel for a distance of approximately 2 inches above the valve. These plaques extended into the mouth of the left coronary artery. On opening the left coronary artery, an organized yellowish white thrombus was found, firmly adherent to the wall and extending from the mouth downward for a distance of approximately $1\frac{1}{2}$ inches. On peeling away this thrombus, considerable arteriosclerotic changes were observed in the endothelial lining of the coronary artery. It was impossible to pass a very fine probe into the artery because of the thrombus. The right coronary artery was patent and free throughout, allowing free passage of the probe, but, when the artery was opened there were observed, for a distance of approximately 2 inches from its mouth, scattered small areas of endothelial arteriosclerotic changes. Microscopic examination revealed no evidence of myocardial damage, either old or recent.

DISCUSSION

This report concerns a 25-year-old white man whose history indicated that he had had angina pectoris for approximately four weeks, and then developed a sudden episode of syncope, from which he recovered quickly. The physical findings were essentially normal. After this acute episode he continued to have angina pectoris at rest (decubitus) for another four weeks and died suddenly one morning while in bed. French and Dock¹ state that more than 100 fatal cases of coronary arterial disease occurring in young soldiers between the ages of 20 and 36 years have been reported since the beginning of the war. In their excellent survey covering 80 such cases, they concluded that the basis of the coronary artery disease in all cases was arteriosclerosis. There was no predilection for any race or national origin; presumably the most striking predisposing factor was overweight, which was present in 91 per cent of the subjects. Our patient showed definite arteriosclerotic disease which involved both coronary arteries and also the ascending arch of the aorta. He was approximately 20 pounds overweight. Another interesting finding reported by French and Dock¹ in their series of 80 fatal cases was that recent myocardial infarction was demonstrated in only 15 of these cases. Fibrous myocardial scars with or without fresh necrosis were found in 39 cases. As a result of these findings, they postulated that coronary arteriosclerosis, or coronary occlusion without myocardial infarction, is the cause of death in younger men more frequently than in older patients. The post-mortem examination of our patient showed no evidence either grossly or microscopically of myocardial scars or recent infarction. It is very likely that, rather than true myocardial infarction, in a significant number of cases of coronary artery disease, myocardial ischemia, resulting in an abnormal cardiac rhythm, probably ventricular fibrillation, is the mechanism causing death.

The pathologic findings in our case admirably fit the concepts and conclusions promulgated by Blumgart and his co-workers.² They found that complete coronary occlusion, or considerable narrowing of one or more coronary arteries, may exist with no evidence of myocardial infarction. This could only be true if the occlusion proceeded slowly, allowing sufficient time to elapse for the formation of an adequate collateral coronary circulation. They also showed that 47 patients suffering primarily from angina pectoris, without evidence of valvular disease or arterial hypertension, had old complete occlusion of at least one major coronary artery at post-mortem examination. In our case, the history of true angina pectoris four weeks prior to the first episode of syncope strongly suggests a slowly progressing occlusion of the coronary artery.

It is of interest to speculate about the episode of syncope which brought the patient to the hospital and was followed by a five-week period of angina pectoris at rest. It is probable that the coronary occlusion resulted in a high degree of coronary insufficiency, but not in enough coronary insufficiency to produce a gross myocardial infarction. Myocardial ischemia resulting from the high degree of coronary insufficiency may very well have brought on an abnormal cardiac rhythm resulting in syncope and finally in death. White

and his associates,³ in their study of 497 cases of angina pectoris, reported that in 47 cases the average duration of life after the onset of angina at rest was 2.8 years. They wrote: "Coronary heart disease, whether shown by the angina pectoris of temporary coronary insufficiency or by myocardial infarction with subsequent scarring, is actually . . . , in the majority of cases, an acute or subacute rather than a chronic disease. This conception . . . is a vital one, of tremendous significance both in prognosis and treatment. . . . The natural tendency of the heart to establish an adequate collateral coronary circulation is the answer."

The electrocardiograms deserve brief mention. The first, taken four hours after the syncopal attack, at a time when the patient seemed to be completely recovered clinically except for mild residual, precordial pain, showed only a deep S_1 and an inverted T_3 . There was no evidence of RS-T depressions or of inversions of the T wave in more than one lead, as would be expected in a diagnosis of coronary insufficiency. The second electrocardiogram, taken five days later, showed a small diphasic T_3 and a decrease in the amplitude of S_1 from 5 mm. in the first electrocardiogram to 2 mm. in the second. We do not feel that these changes warrant an electrocardiographic diagnosis of coronary insufficiency. Stewart and Manning,⁴ in a detailed analysis of electrocardiograms taken on 500 members of the R. C. A. F. Air Crew, state that in 432 an S_1 with a mean amplitude of 2.8 mm. was present, and that in 140 of the cases there was a negative or diphasic T_3 . It is unfortunate that our instrument was out of order when we wished to have the patient undergo an exercise test. It is quite possible that an electrocardiogram taken immediately after exercise would have shown evidence of the coronary insufficiency.

SUMMARY

1. Coronary artery disease probably occurs more frequently in young persons than is generally supposed.
2. Both clinical and electrocardiographic findings may be normal.
3. The onset of angina pectoris of effort is the most important single prodromal symptom and should be given careful consideration.
4. A youthful age should not lull the physician into a false sense of security.
5. With the onset of angina pectoris the patient should be considered as acutely or subacutely ill, and so treated as to allow the heart to establish an adequate collateral circulation.

Grateful acknowledgment is made to the Army Museum of Pathology, Washington, D. C., for their pathologic studies on the heart in the case reported.

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THE WOLFF-PARKINSON-WHITE SYNDROME IN ASSOCIATION WITH CONGENITAL HEART DISEASE: COARCTATION OF THE AORTA

REPORT OF A CASE

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ELECTROCARDIOGRAPHIC evidence of a short P-R interval and bundle branch block has been reported in the literature since 1915.¹ In recent years, this syndrome has been recognized and reported more and more frequently. Doubtless, numerous cases have never been reported. Wolff, Parkinson, and White² concluded that this syndrome consisted of functional bundle branch block and an abnormally short P-R interval occurring with paroxysms of tachycardia in otherwise healthy people. Hunter, Papp, and Parkinson³ reported 19 cases of their own and reviewed the 90 previously reported cases. They found that 18 of these patients and three of their own had cardiac disease which was considered incidental. The heart disease reported in association with this syndrome may be classified under the following etiological headings: rheumatic (mitral and aortic disease), syphilitic, hypertensive, arteriosclerotic (coronary), and thyrotoxic. Coexisting congenital heart disease has apparently not been reported.

Mention has been made as to the age at which this syndrome of short P-R interval with bundle branch block has occurred. The youngest patient on record in whom the syndrome occurred was a boy, 4½ years old. This case was reported by Hamburger⁴ in 1929.

This report includes the following unusual features: (1) The patient whose case history is recorded is apparently the youngest patient in whom the Wolff-Parkinson-White syndrome has been reported. (2) It seems likely that this is the first instance in which coexisting congenital heart disease has been recorded.

CASE REPORT

The patient was a white male child born on May 8, 1942. The family history yielded no evidence of cardiovascular disease. The child was delivered normally at term and weighed 7 pounds, 8 ounces. Nothing abnormal was noticed in the nursery at the hospital during the first ten days of his life. When the child was 4 weeks old, he developed an acute upper respiratory infection and was referred to a pediatrician for care. Examination at that time revealed a heart murmur. A roentgenogram of the chest was taken, and the mother was told that the child had an enlarged heart which was due to a congenital heart defect. The child made an uneventful recovery from the respiratory infection. On Aug. 14, 1942, another roentgenogram of the chest (Fig. 1) showed marked cardiac enlargement.

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The child remained perfectly well until Aug. 22, 1942, when, at the age of 14 weeks, he had a spell in which he "became pale and acted as if he were in a half-faint; his heart was pounding and he was blue around the mouth." Hospitalization was recommended, and on admission at 6 P.M. the child was noted to be dyspneic, pale, slightly cyanotic, and "covered with a cold sweat." The apex beat was regular but very rapid and uncountable. There was a loud systolic murmur at the second intercostal space parasternally. There was also a systolic murmur at the apex, not transmitted. The blood pressure was 98/82 in the right arm and 110/84 in the left arm. The liver was $1\frac{1}{2}$ fingerbreadths below the ninth costal cartilage and was soft. There was no edema. At 8:30 P.M. the child looked better. His color was good, and there was no dyspnea. The heart rate was 147 per minute. There was a moderate blowing systolic murmur at the pulmonic area and a slight systolic murmur at the apex. The heart size was described as "huge." The following diagnosis was made: (1) paroxysmal tachycardia, and (2) probable congenital heart disease.



Fig. 1.—Routine roentgenogram of the chest, Aug. 14, 1942. Note the marked cardiac enlargement.

On Aug. 23, 1942, an electrocardiogram taken after the subsidence of rapid heart action was interpreted as "showing resemblance to the electrocardiogram found in adults with coronary artery disease during anginal pain. There was left axis deviation, sinus tachycardia, and S-T-segment and T-wave abnormalities resembling coronary insufficiency" (Fig. 2). The possibility of a coronary anomaly was considered. Attention was called to the fact that the cardiac enlargement, and S-T-segment, and T-wave abnormalities could possibly be the effects of the tachycardia. The urine was negative. The blood count disclosed a hemoglobin of 73 per cent; erythrocytes, 4,100,000; leucocytes, 12,550, of which 41 per cent were neutrophils, 49 per cent were lymphocytes, 8 per cent were monocytes, and 2 per cent were eosinophiles. A repeat electrocardiogram on Aug. 24, 1942, was exactly the same as the one taken the previous day. There were no further attacks of tachycardia; the child improved and was permitted to go home after two days of hospitalization.

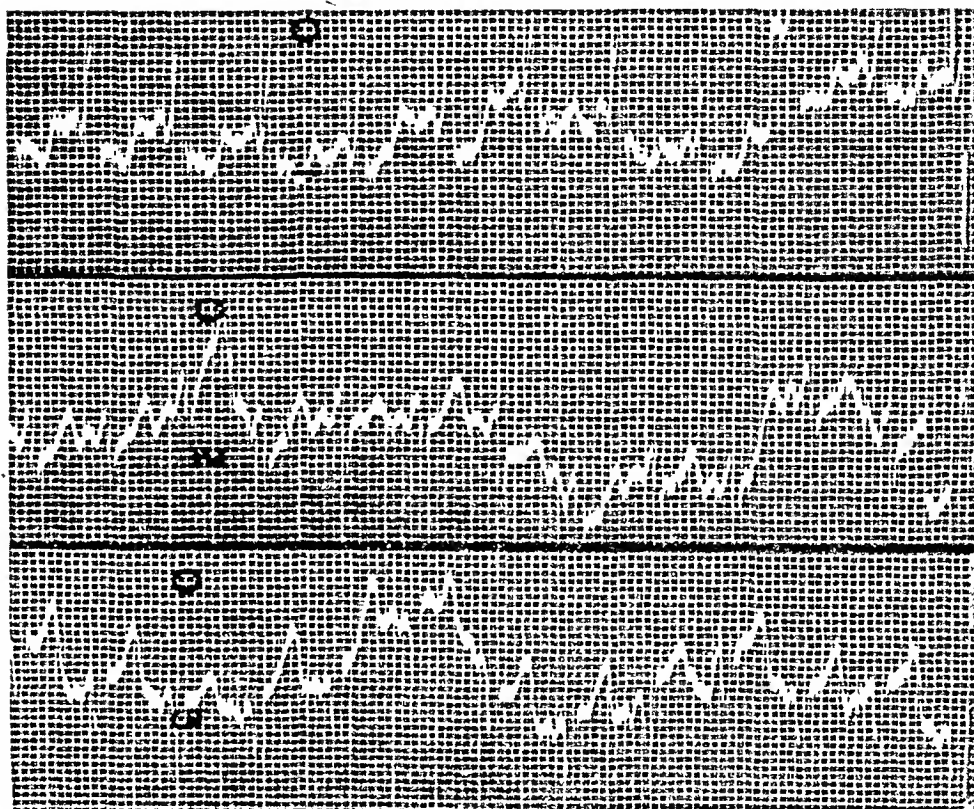


Fig. 2.—Aug. 23, 1942; see text for details.

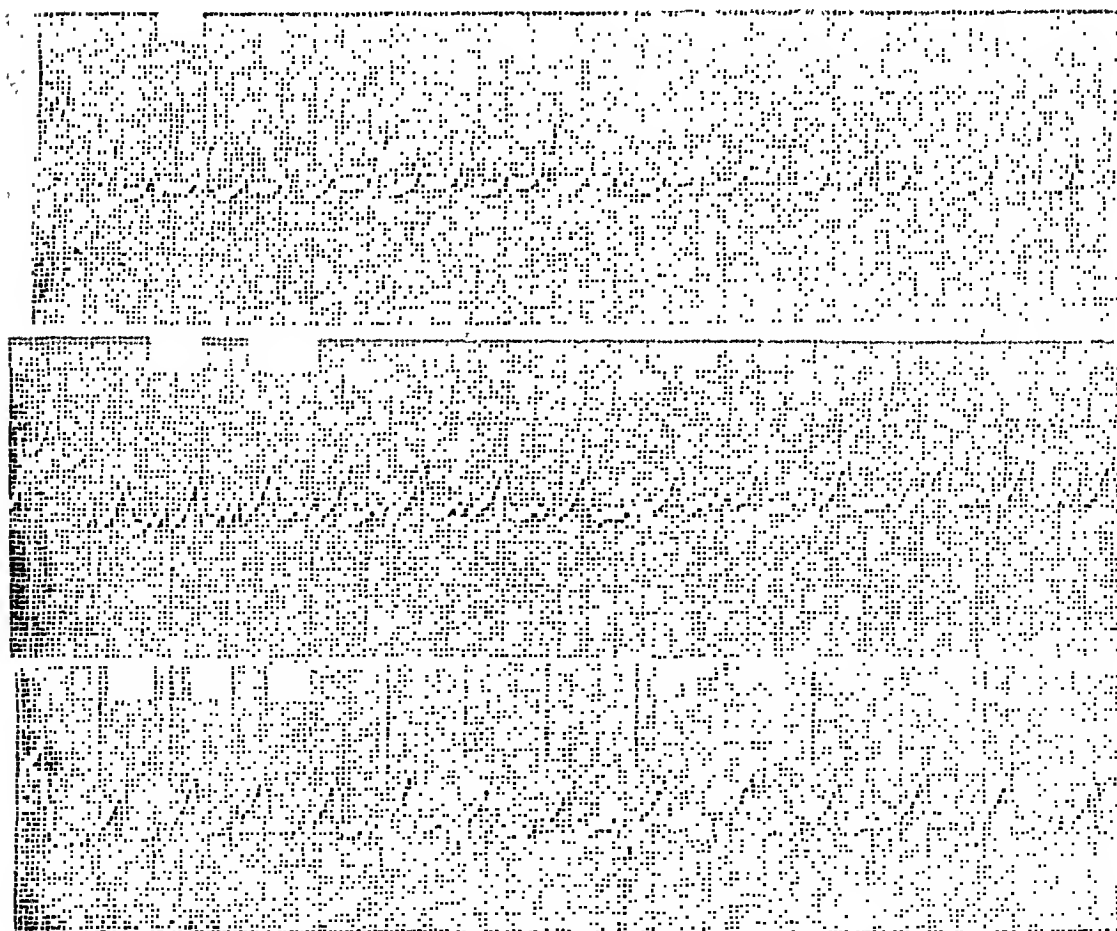
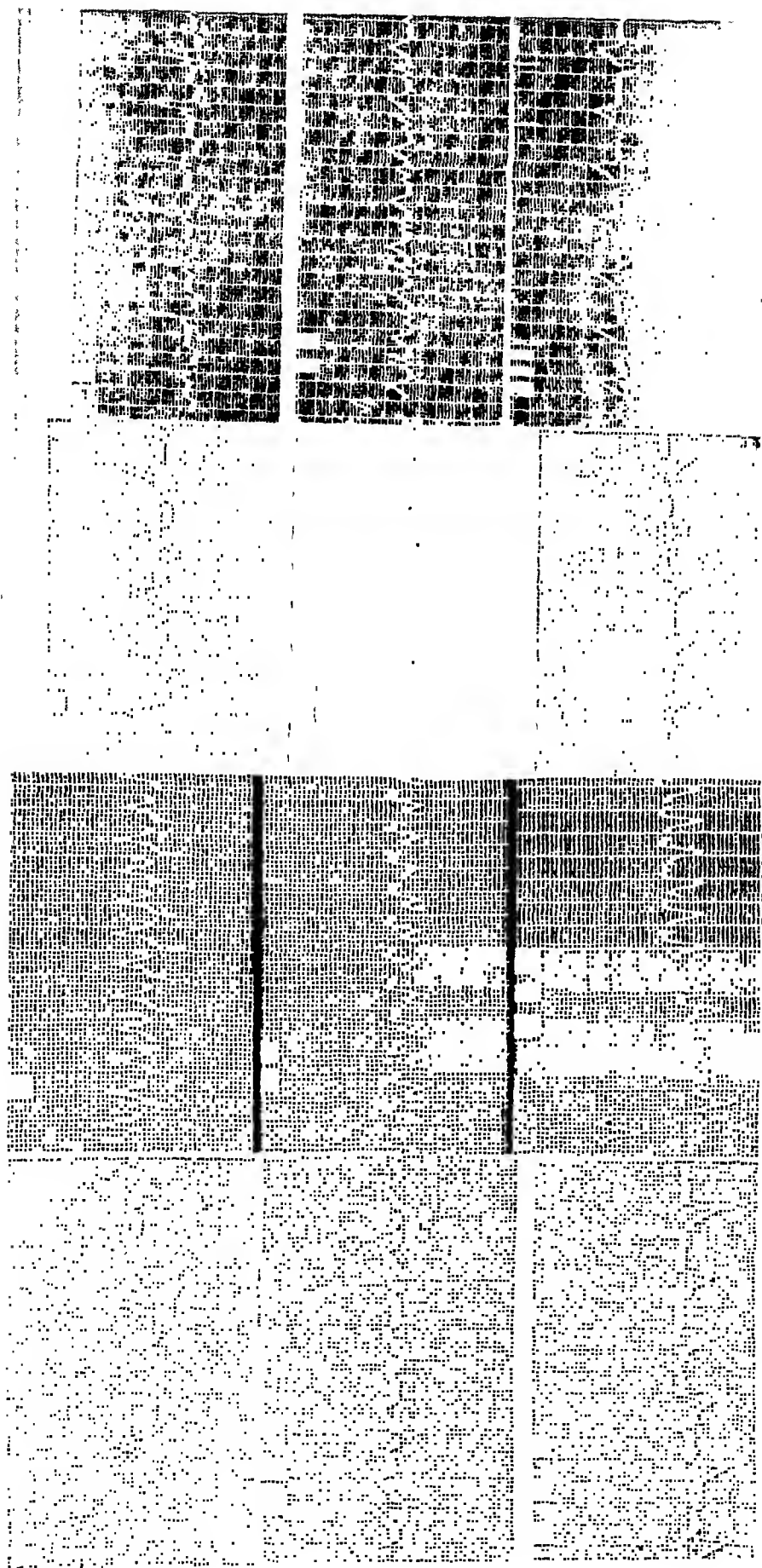


Fig. 3.—Oct. 4, 1944; the Wolff-Parkinson-White syndrome.



A.

B.

C.

D.

Fig. 4.—A, Dec. 6, 1941: normal P-R interval and normal QRS duration. Note abnormal S-T segments and T waves in Lead III. B, April 17, 1945: paroxysmal auricular tachycardia; rate 225. C, April 18, 1945: normal P-R interval and QRS duration after quinidine. Note persistent S-T-segment and T-wave changes. D, June 22, 1945: Wolf-Parkinson-White syndrome present.

From that time until April 25, 1945, the child was in good health, with the exception of "short attacks of rapid heart beat," which were noted by the mother, a former student nurse. She stated that these attacks seemed to terminate spontaneously. On Oct. 4, 1944, the child was brought into the office for a routine physical examination. An electrocardiogram taken at this time showed the characteristic tracing of the Wolff-Parkinson-White syndrome (Fig. 3). On Dec. 6, 1944, a routine electrocardiogram showed a normal P-R interval and a normal duration of the QRS complex. There were, however, S-T-segment and T-wave abnormalities (Fig. 4, A). On April 17, 1945, the child became pale and dyspneic and was brought into the office by his mother, who said that she was certain

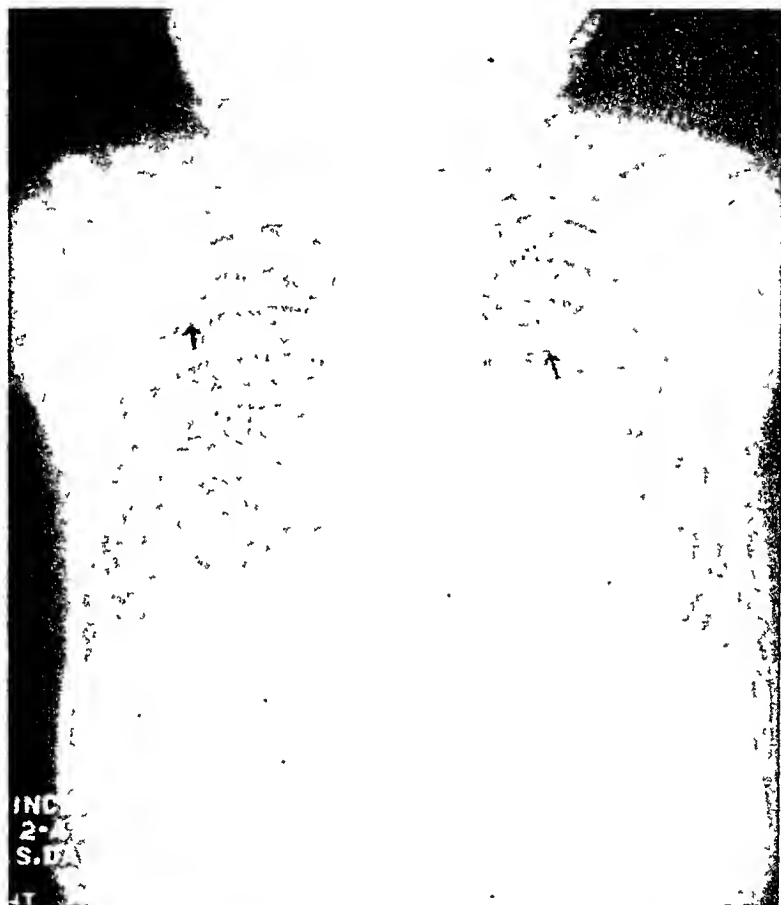


Fig. 5.—Roentgenogram of the chest, June 22, 1945. See text for detailed description. Erosion of lower ends of ribs (black arrows).

"that a spell was coming on." She remarked that the heart was pounding and beating very rapidly. An electrocardiogram taken at that time showed paroxysmal auricular tachycardia with a rate of 225 (Fig. 4, B). The child was given $\frac{3}{4}$ grain of quinidine sulfate and the mother was instructed to repeat this dosage every three hours until the heart rate slowed. However, within one hour after the initial dose of quinidine, the tachycardia disappeared. An electrocardiogram taken the next day showed a normal P-R interval and a normal duration of the QRS complex. The S-T-segment and T-wave abnormalities persisted in this tracing (Fig. 4, C). Since that time numerous spells of tachycardia have been aborted by the use of only $\frac{3}{4}$ grain of quinidine sulfate.

Physical examination of the child on June 22, 1945, revealed a slight bulge over the precordium and marked enlargement of the heart to the left on percussion. There was a moderate blowing systolic murmur at the pulmonic area and a slight systolic murmur at the apex. The aortic second sound and the pulmonic second sound were markedly accentuated. The blood pressure was 130/60 in the right arm and 120/60 in the left arm. The electrocardiogram was typical of the Wolff-Parkinson-White syndrome (Fig. 4, D). A roentgenogram of the chest on June 22, 1945 (Fig. 5), was interpreted by Dr. K. S. Davis,

St. Vincent's Hospital, as follows: "There is marked enlargement of the heart shadow especially in the region of the left ventricle. There is also seen some notching at the lower ends of the ribs and there is almost a complete absence of the shadow of the aortic arch. Roentgen diagnosis: Coarctation of the aorta."

DISCUSSION OF THE ELECTROCARDIOGRAMS

The first tracings, shown in Fig. 2, are, I believe, actually characteristic of the Wolff-Parkinson-White syndrome. The left axis deviation, S-T-segment changes, and T-wave abnormalities mentioned were all part of the pattern of bundle branch block. Certain features of this initial tracing were perhaps justifiably misinterpreted, for it is only by comparison with later tracings that one can recognize the pattern present. Levine⁵ has called attention to the errors made in the interpretation of electrocardiograms taken on infants. The restlessness and muscular activity of children and their movement of the lead wires cause many artifacts, which so distort the tracing that an accurate interpretation is often impossible. In this particular case, it was only after the child was old enough to cooperate that electrocardiograms were satisfactory enough to show the Wolff-Parkinson-White syndrome clearly (Fig. 3). Subsequent tracings revealed that at times the cardiac impulse followed the normal conduction pathway through the heart, as was evidenced by a normal P-R interval and a normal QRS duration (Fig. 4, A). The association of paroxysmal auricular tachycardia with this syndrome was demonstrated (Fig. 4, B). The pattern (Fig. 4, B) was seen to have reverted to a normal rate following the period of tachycardia on the previous day, after the administration of $\frac{3}{4}$ grain of quinidine sulfate (Fig. 4, C). The S-T-segment and T-wave abnormalities in this tracing were no doubt an aftereffect of the paroxysmal tachycardia.

COMMENTS

While the Wolff-Parkinson-White syndrome has been considered benign by most investigators, it is a generally accepted belief that paroxysms of tachycardia, to which these patients are susceptible, can cause heart failure and even lead to death. Any paroxysmal tachycardia which lasts long enough may lead to cardiac decompensation. Therefore, in those cases where cardiac disease coexists, the person prone to attacks of paroxysmal tachycardia is confronted with a definite hazard. The prognosis will vary with the ability of the physician or patient to stop the tachycardia promptly. Inability to terminate the rapid heartbeat will no doubt cause more rapid failure in an already diseased heart to which this load is added than in a normal heart. It is not unreasonable to state that the Wolff-Parkinson-White syndrome in association with a normal heart may be considered benign; however, its occurrence in association with other heart disease certainly alters the prognosis.

The Wolff-Parkinson-White syndrome has been attributed to the existence of an aberrant conduction bundle between the auricles and ventricles.⁶ If this theory be accepted, then we have in the case presented here not only an anomalous conduction system in the heart, but also a congenital heart lesion. This conclusion certainly would be in keeping with the well-known fact that congenital defects which occur are likely to be multiple.

An interesting feature of the case presented here is the erosion of the ribs, as seen in the roentgenogram, occurring in a 3-year-old child. Roesler⁷ states that the youngest patient in whom this sign was reported was 6 years of age.

CONCLUSIONS

1. This report records the occurrence of the Wolff-Parkinson-White syndrome in an infant at the age of 14 weeks. This is apparently the youngest patient with this syndrome on record.

2. The occurrence of a congenital heart lesion in association with the Wolff-Parkinson-White syndrome is also reported.

3. Electrocardiograms showing the typical Wolff-Parkinson-White pattern and the paroxysmal auricular tachycardia associated with it are presented. The presence of a normal P-R interval and a normal QRS duration in some of the tracings shows that the cardiac impulse followed the normal conduction pathway through the heart some of the time.

4. The beneficial effect of quinidine sulfate in this case was demonstrated.

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A CASE REPORT OF SIMILAR SYMPTOMS PRODUCED BY HYPERACTIVE CAROTID SINUS REFLEX, ANGINA PECTORIS, AND MYOCARDIAL INFARCTION

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IN RECENT years the hyperactive carotid sinus reflex has received increasing clinical attention. Its mechanism and the syncopal syndrome produced by the vagal, depressor, or cerebral type of reflex have been thoroughly studied and described.¹⁻³ There have also been a number of reports of unusual symptomatology,⁴ although in most of these syncope is a prominent feature.

The numerous symptoms most frequently associated with this syndrome are mediated through the autonomic nervous system. These are summarized in Table I, which is taken from Ferris, Capps, and Weiss.²

TABLE I. SYMPTOMS DIRECTLY RELATED TO THE CAROTID SINUS MECHANISM

Carotid sinus reflex syncope may be: 1. Vagal type 2. Depressor type 3. Cerebral type		(Fainting, dizziness, weakness
		(Convulsions: contralateral ¹ bilateral ¹
	Central	(Amnesia, cataplexy (Sleeplike state (Fatigue, weakness
	Ocular	(Pupillary changes (Strabismus (Lacrimation
	Respiratory	(Hyperpnea (Apnea (Yawning (Sighing
	Gastrointestinal	(Gaseous eructations (Nausea, vomiting (Increased peristalsis
	Vasomotor	(Hypotension (Peripheral constriction (Peripheral dilatation (Sweating
	Cardiac	(Bradycardia (Arrhythmia (Palpitation
	Extremities	(Numbness, tingling (Convulsions (Babinski's phenomenon

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†Major Glenn died on Dec. 21, 1945.

The hyperactive carotid sinus reflex is frequently associated with numerous other pathologic conditions, both local and general.^{1, 5, 6} Weiss et al.¹ noted that "in 7 of 17 patients subject to the vagal type of syncope there was clinical evidence of degenerative change in the heart, and in the group as a whole there was a high incidence of generalized cardiovascular change." Sigler^{5, 6} pointed out that the hyperactive carotid sinus cardio-inhibitory reflex occurs most frequently and in highest degree in patients with coronary artery disease. He has graded the response on the basis of the degree of heart slowing, but apparently he did not commonly encounter syncope. In his opinion the hyperactive cardio-inhibitory reflex occurs with such frequency in these patients that testing for it aids in the diagnosis of coronary artery disease. Conversely, a syndrome simulating angina pectoris, without coronary artery disease, has also been reported as a manifestation of hyperactivity of the carotid sinus in the early reports of Weiss and his associates, and more recently by Friedman.⁷

The following case report is of unusual interest because both a hyperactive carotid sinus reflex and coronary arteriosclerosis are present and because the same symptoms were produced by both conditions and could not be differentiated.

CASE REPORT

A white officer, 48 years of age, was admitted to this General Hospital on Jan. 11, 1945, from overseas. His history dated back five months, at which time he was overseas when he developed shortness of breath on moderate exertion. Soon thereafter he developed bilateral frontal and parietal headaches, which were associated with exertion and were promptly relieved by rest. Later, he also began to have pain at the angles of both jaws. This pain also occurred with exertion and was promptly relieved by rest. Five weeks later he developed attacks of substernal pain associated with shortness of breath and a feeling of pressure on his chest, as well as pain in the jaws and head. These attacks were also precipitated by exertion and relieved by rest.

After a week or ten days of these attacks, on Oct. 7, 1944, while walking, he developed a severe substernal pain which radiated to the left posterior supra scapular area and was severe enough to cause him to break out in a cold sweat. The pain lasted about five minutes. Subsequently he was admitted to a hospital.

Physical examination at that time revealed no cardiac or other abnormality. The blood pressure was 130/74. Laboratory tests on several occasions showed the red blood cell count, hemoglobin, white blood cell count, differential, urinalysis, and sedimentation rate to be normal. X-ray examination showed a normal cardiac silhouette. An electrocardiogram taken the day following admission (Fig. 1, *a*) showed an inverted T₁ and a deeply inverted T₂, but no significant changes in the S-T segments. He was considered to have a coronary occlusion, and was treated with complete bed rest. During this time he had three mild attacks of substernal pressure with radiation to the left shoulder. One attack occurred while he was sitting on the edge of the bed, and another occurred while he was helping to make his bed. The attacks were quite brief and required no medication. A second electrocardiogram (Fig. 1, *b*) taken nine days after the first showed reversion of the T waves to their normal upright configuration. Subsequent electrocardiograms continued to show only left-axis deviation. A diagnosis of acute coronary thrombosis was made. After five weeks, evacuation was begun, first to Paris, subsequently to England. There, after a short period of bed rest, he was allowed up and around more freely.

While in a hospital in England, on Dec. 20, 1944, while lying in bed he developed another acute severe substernal pain, which again caused him to break out in a cold sweat. Again there was radiation to the left scapular region, but there was no associated jaw or head pain. This time the pain persisted for about one and one-half hours, and he was given an

intravenous injection for relief. Unfortunately, although this was the most severe attack he had had, no electrocardiograms were taken. He left for the United States on December 23 and arrived at a hospital in this country on January 4, having had no symptoms in the interim. An electrocardiogram taken sixteen days after the severe attack showed only left axis deviation. The patient was then transferred to this General Hospital.

The family history revealed no cardiovascular or renal disease. His mother died at the age of 65 years from an unknown cause. His father was living and well at the age of 74 years.

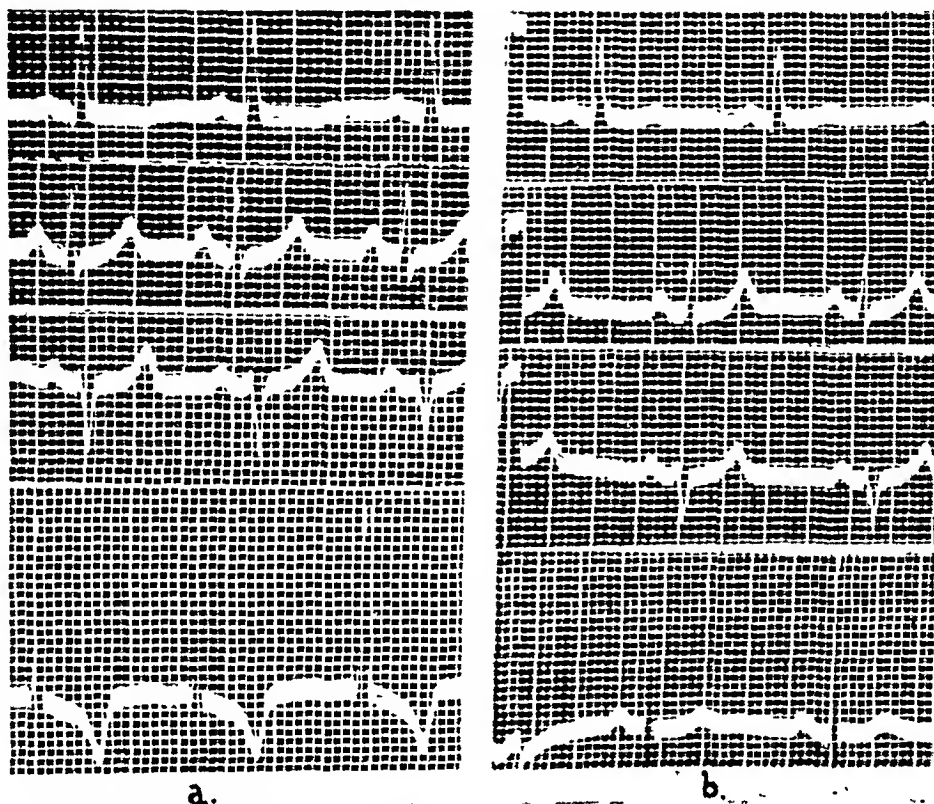


Fig. 1.—*a*, Electrocardiogram taken Oct. 8, 1944, twenty-four hours after first severe attack of substernal pain. Note inverted T_1 and T_4 . *b*, Electrocardiogram taken Oct. 17, 1944. The voltage of T_1 is slightly low, though in subsequent electrocardiograms it was entirely normal.

The patient had influenza complicated by pneumonia in 1918. He had a right herniorrhaphy in 1942. In January, 1944, he developed a left peroneal nerve palsy, for which he was being treated as an outpatient. One night when sitting by the fire he noticed that he had burned the calf of his left leg. The burn required hospital care, and during this time he received injections of thiamine and liver extract, following which the palsy gradually disappeared. During the two years previous to his present hospitalization, the patient had lost about 45 pounds in weight. This weight loss had been gradual and unassociated with any symptoms.

Physical examination at the time of admission to this hospital showed an individual who appeared to be older than his stated age. He was well developed and fairly well nourished, though he showed evidence of some weight loss. There was a scar from an old burn on the lateral aspect of his left leg. The ocular fundi showed a slight increase in tortuosity and streaking of the arteries. The brachial arteries were readily palpable but not tortuous. There was no apparent venous distention. The heart was of normal size. The sounds were slightly distant but of good quality. A_2 was louder than P_2 . No murmur was audible, but about one month after admission one observer noted a very soft systolic murmur

localized at the apex. The blood pressure was 130/80. The remainder of the examination, including that of the neck, was negative.

The results of laboratory studies were as follows: hemoglobin, 109 per cent; red blood cells, 4,860,000; white blood cells, 7,350; neutrophils, 53; lymphocytes, 45; eosinophils, 2. The sedimentation rate was 4 mm. per hour by the Wintrobe method. A Fishberg renal concentration test showed specific gravities of 1.028, 1.027, and 1.028. The urinalysis was essentially negative. The blood Kahn test was negative.

An electrocardiogram taken on admission showed merely a left axis deviation. An electrocardiogram taken after exercise revealed a sinus tachycardia of 120; otherwise there was no change.

The interpretation of the x-ray examination of the chest was: "The heart does not appear enlarged. Aorta is slightly elongated and tortuous, and there is a small calcareous plaque in the arch. The lungs appear clear."

During his first month in the hospital, the patient was ambulatory, without great limitation to his activity. He experienced three mild attacks of head and jaw pain, and slight shortness of breath. During or after these attacks he experienced palpitation. Exertion was not uniformly a precipitating factor.

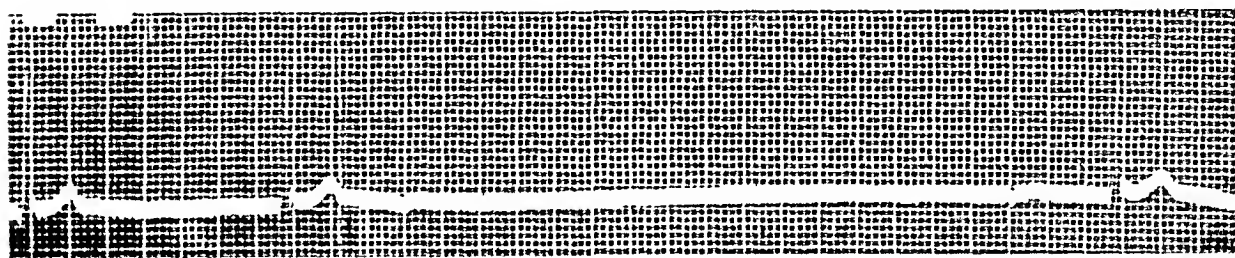


Fig. 2.—(Lead IVF) Asystole of 4.5 seconds' duration following right carotid sinus stimulation. Original rate was 85 per minute. (Date Feb. 10, 1945.)

On one occasion while the patient was being examined, it was noted that he had a somewhat flushed face, which appeared to be due to a tight collar on his shirt. This, together with the unusual symptomatology of jaw pain and head pain, suggested a possible hyperactive carotid sinus syndrome. With carotid pressure on either side, the patient spontaneously stated that symptoms of jaw pain and frontal headache similar to his previous symptoms were produced. At this time his pulse rate, which had been 60, dropped to 46 per minute.

Carotid sinus stimulation was subsequently employed on several occasions while electrocardiographic tracings were being taken and invariably produced attacks of pain of varying intensity. On each occasion stimulation of either carotid sinus produced a high degree of cardiac inhibition, though stimulation of the right sinus produced more slowing of the heart rate. The rate dropped from about 85 per minute to about 50 per minute. Fall in blood pressure (130/76 to 100/70) was transient and brief, and not uniformly produced. Syncope was never produced, even when stimulation was maintained for as long as sixty seconds. On one occasion while the right sinus was being stimulated, the patient had asystole lasting 4.5 seconds (Fig. 2) and experienced the most severe symptoms. He complained of head pain, jaw pain, dizziness, shortness of breath, and "tingling all over." All his symptoms were reproduced except the substernal pain.

The electrocardiogram (Fig. 2) during the 4.5-second asystole shows both sinus arrest and auriculoventricular block. No other changes were produced by the carotid sinus stimulation. There was little doubt that he had a hyperactive carotid sinus reflex of a type predominantly cardio-inhibitory (vagal).

These findings on carotid sinus stimulation made it difficult to determine whether all the symptoms were due to angina pectoris caused by coronary insufficiency and myocardial ischemia, or whether some or most of the symptoms were due to a hyperactive carotid sinus. The fact remained, however, that stimulation of the carotid sinus reproduced all symptoms except the substernal pain which the patient had had on previous occasions.

With some evidence of generalized arteriosclerosis, it was not at all improbable that the patient had coronary arteriosclerosis. He may have had a myocardial infarction which had produced only transient electrocardiographic changes and at this time showed no residual changes.

On Feb. 22, 1945, the patient appeared before an Army Retiring Board. Three days later he went fishing, in a motorboat. He had not exerted himself a great deal, but had been in the sun for several hours. Just before leaving the boat he was seized by a severe pain in the substernal region and felt pain also in the neck and in the jaws. Previous to returning to the hospital, within two hours of the attack, he had taken two nitroglycerin tablets, with some relief of his pain.

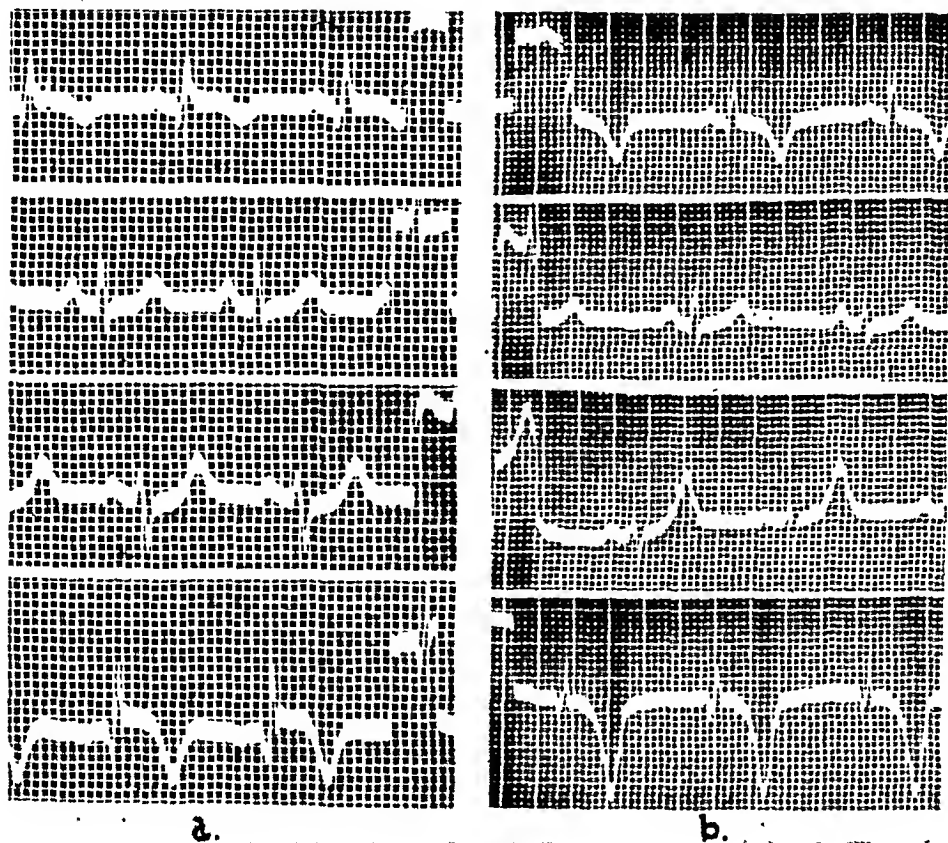


Fig. 3.—*a*, Electrocardiogram taken Feb. 26, 1945, twenty-four hours after a severe attack of substernal pain and pain in neck and jaws. *b*, Electrocardiogram taken April 2, 1945. The records are typical of acute (*a*) and residual (*b*) changes of anterior apical myocardial infarction.

On examination he had an anxious appearance. The pulse was regular and of good quality. The rate was 82 per minute. The examination of the heart was negative. The blood pressure was 138/92. Immediately after examination he was given $\frac{1}{4}$ grain of morphine and placed on bed rest. In about an hour and one-half a second dose of morphine was administered and the pain gradually disappeared, though he required another $\frac{1}{4}$ grain of morphine. He continued to have some aching and pressure in the precordial region for three to four days. Subsequently he had no complaints. Examinations of the heart after this acute episode were not significant. At no time was a friction rub heard, and at no time did the blood pressure fall below 120/80. The average was 136/80.

Laboratory studies on the day following this attack showed a white blood cell count of 10,150 per cubic millimeter, with a differential count of 82 per cent neutrophils and 18 per cent lymphocytes. The white count varied between 8,000 and 11,000 for the next four weeks. The sedimentation rate was 6 mm. per hour on the day following the attack and rose

to a peak of 26 mm. per hour on the ninth day following the attack. Following this peak it returned to normal levels.

Electrocardiographic changes were characteristic of the Q_1T_1 anterior apical type of infarction. The record obtained on the morning after the acute episode (Fig. 3, a) showed a short Q_1 , elevation of the S-T₁ and S-T₄ segments, and slight depression of the S-T₂ and S-T₃ segments. T₁ and T₄ were deeply inverted. By March 6, the S-T segments had become isoelectric, but T₁ and T₄ had become more deeply inverted. This degree of inversion increased progressively and remained high until discharge (Fig. 3 b).

After the mild pains of the first few days, the clinical course was essentially asymptomatic. He was given phenobarbital and aminophylline three times daily. After three weeks of bed rest he was allowed up slowly and progressively. He remained asymptomatic except for slight tiredness after walking, but his strength rapidly returned. An x-ray film of the chest taken on March 29 showed a slight relative prominence of the left ventricular portion of the heart but was otherwise negative. He was discharged to his home on April 5, 1945.

DISCUSSION

There can be little doubt that while under our observation the patient had one quite typical myocardial infarction, probably the result of coronary occlusion on the basis of coronary arteriosclerotic disease. It is also probable that the episode just prior to his first hospitalization overseas represented more than a transient myocardial ischemia and may have been an infarction, though the only objective evidence to support this was the one electrocardiogram showing inverted T₁ and T₄ waves, which had become essentially normal, except for left axis deviation, in the electrocardiogram taken nine days later. Sixteen days following his second, and most severe, bout of pain overseas, an electrocardiogram was again, or still, normal except for left axis deviation.

The symptoms in these three attacks were similar to those in numerous other attacks he experienced during the month prior to overseas hospitalization and during his subsequent course under observation, except that the substernal pain was more severe. Many of these attacks were apparently precipitated by effort, though some definitely were not. Whether they represented attacks of true angina pectoris or hyperactive carotid sinus reflex is a matter for conjecture. They were not entirely typical of either, but had some of the features of both. The fact that stimulation of the carotid sinus region reproduced the symptoms indicates that this reflex at least was hyperactive, but there is also evidence that coronary disease was present. An infarction could hardly be attributed to a hyperactive carotid sinus (cardio-inhibitory) reflex.

To enter into a physiologic discussion of the mechanism of production of these symptoms in this particular case is beyond the scope of this paper. Suffice it to say that probably the same effector end organs were activated both by the reflexes initiated by myocardial ischemia and by the hyperactive carotid sinus reflex. Though the carotid sinus reflex is mentioned as one of the mechanisms affecting myocardial nutrition in Gross and Sternberg's report of 15 cases of myocardial infarction without demonstrable occlusion of the coronary arteries,⁸ this etiological factor has not been proved in any case. In discussing reflexes, Gross and Sternberg state: "Sudden death, which sometimes occurs, may be due to cardiac standstill resulting from extreme vagal stimulation, but it is

also possible that such vagal stimulation may produce reflex coronary vasoconstriction and myocardial ischemia."

SUMMARY

1. A case report is presented in which a hyperactive carotid sinus reflex and coronary arteriosclerosis were present.
2. The fact that symptoms produced by stimulation of the carotid sinus were similar to the patient's spontaneous symptoms made it impossible to determine whether they were produced by the hyperactive carotid sinus reflex or were true angina pectoris resulting from myocardial ischemia.
3. During observation the patient had a typical myocardial infarction.

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Abstracts and Reviews

Selected Abstracts

Moses, W. R.: **The Early Diagnosis of Phlebothrombosis.** *New England J. Med.* 234: 288 (Feb. 28) 1946.

The high incidence of phlebothrombosis of the leg veins and the importance of early diagnosis are stressed. A simple clinical test is described for differentiating early phlebothrombosis from lesions simulating it. The test consists of two maneuvers. The first maneuver comprises a careful search for tenderness in the deep posterior calf by direct compression with the fingertips in the anteroposterior direction. The second maneuver consists in compressing the calf between the fingers and the palm in a lateral direction. In early phlebothrombosis this lateral compression is painless or relatively so, as compared with the first maneuver. The great majority of lesions simulating incipient thrombosis are accompanied by considerable tenderness on lateral compression. The findings in a case of peripheral neuritis, however, may be similar to those in a case of phlebothrombosis; accordingly, a brief neurological examination of the extremity is included as the third maneuver. NAIDE.

Lange, K., and Loewe, L.: **Subcutaneous Heparin in the Pitkin Menstruum for the Treatment of Experimental Human Frostbite.** *Surg., Gynec. & Obst.* 82: 256 (March) 1946.

Previous animal experimentation demonstrated that the timely use of heparin prevented gangrene, whereas untreated control animals uniformly developed gangrene as a result of experimentally induced frostbite. Only after at least seventy-two hours does organization of the erythrocytes occur in the smaller vessels. The use of heparin early in this prethrombotic stage prevents organized thrombi from forming. The authors applied these findings to a study of the use of heparin in eight human volunteers in whom artificial frostbite was produced. Small areas of frostbite were produced by the use of dry ice. Heparin in Pitkin's menstruum was deposited subcutaneously or intramuscularly. None of the volunteers developed any tissue loss while the control lesions showed central necrosis. The Pitkin menstruum was designed to regulate the release of water soluble drugs and is composed of gelatin, dextrose, glacial acetic acid, and water in definite proportions. NAIDE.

Stevens, C. D., Kotle, J. H., Smith, C. C., and McGuire, J.: **The Treatment of Human Hypertension With a Kidney Extract.** *Am. J. M. Sc.* 211: 227 (Feb.) 1946.

The authors report the treatment of four carefully controlled, hypertensive patients with a kidney extract which contained no renin or angiotoninase activity. A concentrated extract was prepared which was of relatively low toxicity.

Three of the patients showed during treatment a noteworthy fall in blood pressure, associated with fever. The fourth patient, who developed little fever, demonstrated only a slight depressor effect. However, blood pressure measurements made during the afternoon peak of the fever were not appreciably lower than those made in the morning before the temperature began to rise. The two subjects who demonstrated the greatest fall in blood pressure exhibited hypersensitivity reactions and developed serum precipitins. The fall in blood pressure during thiocyanate administration was of the same magnitude as that following the adminis-

tration of kidney extract in two cases but was not as marked as in the third patient whose blood pressure dropped.

The results obtained with this kidney extract do not recommend its use. Until the toxic effect of such kidney extracts can be eliminated, their therapeutic evaluation will be difficult and the mechanism of their action will be undetermined.

NAIDE.

Master, A. M., and Eichert, H.: *Functional Paroxysmal Auricular Fibrillation*. Am. J. M. Sc. 211: 336 (March) 1946.

By the term "uncomplicated or functional paroxysmal auricular fibrillation" is meant that type in which no evidence of organic heart disease can be demonstrated. This type of arrhythmia was not infrequently encountered in Naval personnel. The authors report a series of five cases in which the chief presenting symptom was "palpitation" or "pounding of the heart." They suggest that many cases which are diagnosed clinically as paroxysmal tachycardia are actually cases of paroxysmal auricular fibrillation. They also stress the importance of psychogenic or nervous factors in the production of paroxysmal auricular fibrillation. This was especially true among susceptible individuals who had been placed under unusual stress and strain.

From the standpoint of treatment, removal of the cause is important, particularly any factor disturbing the patient's mental equilibrium. Excessive exertion, mental and physical fatigue, lack of sleep, overindulgence in tobacco and coffee, and gastric distention should be avoided. They have obtained good results by the administration of digitalis or quinidine. In the absence of quinidine, they have administered potassium acetate, 1 or 2 Gm. three times daily. It is advisable that patients with this functional arrhythmia should be discharged from the Navy or retained for limited shore duty only.

BELLET.

Groedel, F. M., and Miller, M.: *Esophago-cardiogram*. Exper. Med. & Surg. 4: 26 (Feb.) 1946.

The esophagogram contains waves produced by the movements of the heart. It was studied as the esophago-cardiogram by the following technique. The tube of Einhorn's cardia dilator was introduced into the esophagus up to the cardia of the stomach, its outer end was connected with a microphone, and the system was filled with a few cubic centimeters of air. The microphone recorded on a three-string galvanometer simultaneously with Lead CR, and the heart sounds. The balloon was drawn out slowly, a record being made every 1 or 2 inches.

The esophago-cardiogram obtained with the balloon placed below the level of the left auricle is identical with the phlebogram obtained over the jugular bulb with a loaded receiver bell. It reflects most of the mechanical events occurring during auricular systole and diastole and ventricular systole. The action of the left auricle is represented by a positive a wave, produced by and reflecting the a wave of the vena cava. The ventriculodiastolic part of the esophago-cardiogram forms a v wave or a "v + d" wave. When the end of the tube is placed at or above the level of the auricle, the auricular wave is negative because the receiver balloon records here the movements of the auricular wall. The ta wave, representing probably the closure of the A-V valves, the b waves, caused by the isometric contractions of the ventricles, and the c complex, which reflects the isotonic contraction and ejection phase of the ventricles, are recorded throughout the esophagus.

LAPLACE.

Borchardt, P. R., and Groedel, F. M.: *Intrathoracic Auscultation in the Pneumothorax*. Exper. Med. & Surg. 4: 34 (Feb.) 1946.

In order to determine how the physical character of the heart sounds becomes altered while traveling from the cardiac surface to the surface of the chest, it is necessary to eliminate the lungs and the chest wall and study the heart sounds inside the thorax. Comparison was

therefore made of extrathoracic (chest wall) auscultation and intrathoracic auscultation in about 50 patients with normal hearts. About 20 were examined during the refilling of a therapeutic pneumothorax and the rest were examined during a pneumolysis. Before the operation was started, phonocardiograms were recorded from various points over the precordium. After refilling of a pneumothorax was finished, the needle used for the operation was connected directly with the recording microphone by a 3 to 4 cm. rubber tube. In the patients who had undergone pneumolysis, one of the two cannulae which are inserted after the Jacobaeus operation was closed, and the other was connected directly with the microphone. Simultaneous electrocardiograms were made.

It was found that the heart sounds inside the chest have a sonorous character with frequencies averaging 35 cycles per second in comparison with their high-pitched, metallic quality outside the chest where their frequencies are about 125 cycles per second for the first sound and 100 cycles for the second sound. The additional higher frequencies of the extrathoracic sounds are picked up while the sounds travel from the cardiac surface to the surface of the body.

The first heart sound in the intrathoracic pneumocardiogram consists usually of only four cycles representing, respectively, isometric contraction of the right and left ventricles and opening of the right and left semilunar valves. The first sound may be preceded by a ta-sound (single wave) which originates at the time of closing of the mitral valve. The second sound consists of two and, less frequently, three cycles, recording the closure of the two semilunar valves. The intrathoracic phonocardiogram frequently contains a third heart sound. This demonstrates that the latter actually originates in the heart. The auricular contraction sound preceding the first sound is also frequently seen. LAPLACE.

Aikawa, J. K.: Hypersensitivity and Rheumatic Fever. *Ann. Int. Med.* 23: 969 (Dec.), 1945.

This study consists of a very extensive review of the literature pertaining to the relation of rheumatic fever to hypersensitivity.

Part I is concerned with hypersensitivity, antibodies, serum sickness, allergy, and the interrelation of these phenomena. The evolution of the concepts of this interrelationship is followed through successive reported studies, and the more recent concepts of various authors are presented.

Part II is concerned with the literature which presents evidence for a relation between hypersensitivity and the rheumatic process. The similarity between some manifestations of rheumatic disease and serum sickness is emphasized, as well as the general similarity between histologic changes in rheumatic disease and the proliferative inflammation of connective tissues found in sensitized animals following injection of the specific irritant. Included in the review are reports on the treatment of rheumatic subjects with salicylates and investigations which have been made to determine a rationale for such therapy in terms of immunologic reactions. T. N. HARRIS.

Kety, S. S., and Schmidt, C. F.: The Effects of Active and Passive Hyperventilation of Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output and Blood Pressure of Normal Young Men. *J. Clin. Investigation* 25: 107 (Jan.), 1946.

Both active and passive hyperventilation by normal human subjects is accompanied by a diminution in cerebral blood flow amounting to 33 to 35 per cent (average) of the control volume flow. Carbon dioxide content, carbon dioxide tension, and hydrogen ion content of arterial blood diminish significantly, and the cerebral arteriovenous oxygen difference increases. During active hyperventilation cardiac output increases by an average of 2 per cent whereas during passive hyperventilation cardiac output decreases 11 per cent below the control values. Mean arterial pressure increases 12 per cent above the control during active hyperventilation and 8 per cent above the control during passive hyperventilation. It is of considerable interest that cerebral oxygen consumption is in-

creased by 15 per cent above the control value during active hyperventilation whereas during passive hyperventilation the average change is 0 per cent. The increase in cerebral oxygen consumption during active hyperventilation is attributed to an increase in cerebral metabolic activity incident to the mental effort involved. The reduction in cerebral blood flow during hyperventilation is related to the diminution in carbon dioxide content of the blood thus produced.

FRIEDLAND.

Jager, B. V., and Alway, R.: The Treatment of Acute Rheumatic Fever With Large Doses of Sodium Salicylate, With Special Reference to Dose Management and Toxic Manifestations. *Am. J. M. Sc.* 211: 273 (March), 1946.

The results of the treatment of rheumatic fever by massive doses of sodium salicylate are evaluated. In the adult group of 18 patients, clinical and laboratory evidence of rheumatic activity appeared to vanish in six patients with initial attacks and in five of 12 patients with recurrent episodes. In all of the 18 adult patients, rapid symptomatic improvement occurred within a few days after therapy was begun. There was no fever after the end of the second week. Anemia, which was present in some cases at the time of admission, disappeared in every instance during therapy.

Good results were also obtained in a group of eight children but were not as striking as in the adult group. No serious intoxication appeared in any patient whose plasma salicylate level was less than 400 mg. per cubic centimeter. Some patients were able to tolerate levels above 500 mg. per cubic centimeter for prolonged periods without difficulty. In spite of significant prolongation of the prothrombin time, hemorrhagic manifestations were observed in only one instance.

BELLETT.

Braun, K.: Paravertebral Block and the Electrocardiogram in Angina Pectoris. *Brit. Heart J.* 8: 47 (Jan.), 1946.

Considering the electrocardiogram as a method of evaluating the coronary circulation, the author studied the effect of block of the upper four thoracic paravertebral ganglia in a series of twelve patients who had angina pectoris. Four to seven injections were given at intervals of three to six days. The first injection utilized novocain, while the remainder consisted of novocain and alcohol. Electrocardiograms were taken before and after treatment, and, in seven cases, immediately before and twenty-four hours after the first injection.

Eleven patients had abnormalities of the electrocardiogram before treatment. In three instances, in which the abnormalities consisted, respectively, of bundle branch block, myocardial infarction, and negative T waves in all leads, there was no improvement in the electrocardiogram after block. In eight cases, improvement in the electrocardiogram occurred. Improvement was generally maximal at the end of treatment, although in four cases a positive effect was present twenty-four hours after the first block. The improvement could be explained by increase in coronary blood flow due either to a direct effect of the block or to abolition of reflex spasm accompanying the relief of pain. No consistent parallelism was found, however, between the improvement of the electrocardiogram and the persistence and severity of the anginal pain. In one case the electrocardiogram at first improved, then became more abnormal although the patient was relieved of pain; in other cases, the patients had recurrence of angina although the electrocardiogram improved.

LAPLACE.

Biorck, G.: Hypoxemia Tests in Coronary Disease. *Brit. Heart J.* 8: 17 (Jan.), 1946.

The subject of induction of electrocardiographic changes following the administration of low oxygen mixtures in the diagnosis of coronary artery disease is discussed. An analysis is presented of the results of 350 hypoxemia tests performed on 326 patients, of whom 166 were men and 160 were women. The patients were divided into three groups:

(1) those in whom there was no suspicion of coronary heart disease, (2) those in whom coronary disease was suspected, and (3) those in whom the presence of coronary disease was very probable or certain. The criteria for a positive test were the same as those established by Levy and his associates in 1938. The technique employed was similar to that originally described by Levy and his co-workers, inhalation of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes, except for minor technical modifications of the apparatus which delivered the gas mixture. In attempting to correlate the clinical findings with the electrocardiographic changes produced by the hypoxemia tests, the records were interpreted without any knowledge of the clinical evidence. The incidence of positive tests in Groups 1, 2, and 3 was 3 per cent, 20 per cent, and 30 per cent, respectively. However, when the cases in which there were "coronary" cardiographic changes before the test were excluded from the calculation, the incidence of positive tests in Groups 1, 2, and 3 was 2 per cent, 18 per cent, and 23 per cent, respectively. It was also observed that the test was positive in only 5 of 18 patients who had healed myocardial infarction and still suffered from angina pectoris. In the opinion of the author the results appear to indicate that the value of this test in the diagnosis of coronary disease cannot yet be decided in any final sense at this time.

WENDKOS.

Lyons, R. H., and Burwell, C. S.: Induced Changes in the Circulation in Constrictive Pericarditis. *Brit. Heart J.* 8: 33 (Jan.), 1946.

The physiologic alterations and adaptations which accompany constriction of the pericardium were studied in two patients before and after pericardiolysis. An attempt was made to establish correlations between cardiac output, venous pressure, blood volume, circulation time, and heart rate. Spontaneous fluctuations in the level of the venous pressure, as well as sudden alterations of the venous pressure induced by rapid infusions or rapid phlebotomy, could be correlated only with blood volume and were found to bear no relationship to alterations in the heart rate or cardiac output. Further observations in one case following the alternate use of diuretics and sodium chloride seem to indicate that the elevated venous pressure, which is a conspicuous feature in constrictive pericarditis, is due to mechanisms similar to those which operate in cases of congestive failure without pericardial constriction, such as a rise in blood volume due to retention of sodium. The authors also speculate upon the adaptive mechanisms which occur in constrictive pericarditis and emphasize that a high venous pressure in this condition, unlike circumstances in which diastolic failure of the heart is due to tamponade by fluid in the pericardium, cannot be an effective compensation for the reduced cardiac output. On the other hand, the beneficial effect of tachycardia, either spontaneous or induced, is demonstrated from measurements of cardiac output and venous pressure. The authors also emphasize that since digitalis may induce slowing of the sinus rate, this drug is contraindicated in the treatment of constrictive pericarditis before adhesions are released.

WENDKOS.

Schnitzer, R., and Gutmann, D.: Myxedema With Pericardial Effusion. *Brit. Heart J.* 8: 25 (Jan.), 1946.

In a completely studied case of myxedema associated with marked enlargement of the heart shadow and with few signs or symptoms of cardiac failure, the authors present data which seemed to confirm the view of previous observers that part of the cardiac enlargement in "myxedema heart" is to be ascribed to an associated pericardial effusion. In their case, the presence of pericardial effusion was established by paracentesis with removal of 60 c.c. of straw-colored fluid from the left side of the pericardium. Serial electrocardiograms were made during the period of observation. The disappearance of the low voltage of all the electrocardiographic deflections in the standard limb leads and the return of the heart shadow to normal diameters following treatment with thyroid extract is explained by the authors as the result of dissipation of the fluid surrounding the

heart. The amplitude of the auricular and ventricular deflections in the tracings made before, during, and after treatment with thyroid extract bore no relationship to the heart rate, the increase in voltage occurring without any cardiac acceleration. WENDKOS.

Lequieme, J., and Denolin, H.: Changes in the Coronary Circulation in the Course of Aortic Insufficiency in Young Subjects. *Arch. d. mal. du cœur.* 38: 225 (Sept.-Oct.) 1945.

Three cases are reported in which attacks of angina pectoris occurred in patients who had rheumatic aortic insufficiency. The patients were 14, 15, and 29 years old, respectively. The attacks of pain were independent of physical exertion and occurred most frequently at night. They were usually accompanied by tachycardia and increase in blood pressure. Electrocardiograms were made during the attacks and revealed transient S-T interval deviation similar to the changes induced by effort in patients who have coronary disease. The various explanations which have been offered as to the cause of anginal pain in the presence of aortic insufficiency are discussed. The author believes that his observations favor the view that the pain results from a disproportion between the coronary circulation and the work of the heart. LAPLACE.

Broustet, P., Bergouignan, M., and Leger, H.: Flutter and Auriculo-Ventricular Dissociation in a Patient With Myopathy. *Arch. d. du cœur.* 38: 212 (Sept.-Oct.) 1945.

The case is presented of a man, aged 54 years, who had long standing progressive muscular atrophy of idiopathic type. At an advanced stage of the disease but while he was still able to work, the patient began to have manifestations of cardiac insufficiency. A physician noted that the pulse rate was 40 per minute, the blood pressure was 220/110, and the heart was enlarged. After a month of treatment, the patient returned to work, but five months later he was admitted to the hospital because of two episodes of syncope. An electrocardiogram revealed auricular flutter with a rate of 200 per minute. The ventricular complexes were relatively normal but occurred at a rate of 40 per minute and had no constant time relationship to the auricular waves. There were no further manifestations of cardiac insufficiency and, when last observed, the patient had no symptoms except those caused by his muscular dystrophy. No subsequent change occurred in the electrocardiogram and even full digitalization failed to influence the constant auricular and ventricular rates. The cause of the heart disease responsible for the arrhythmia was not determined; the authors consider the possibility that it may have been related to the skeletal myopathy. LAPLACE.

Jourdan, F., Froment, R., Gallavardin, L., and Baud, A.: Three Observations on Chronic Experimental Nodal Rhythm by Surgical Ablation of the Sinus Node. *Arch. d. mal. du cœur.* 38: 197 (Sept.-Oct.) 1945.

The authors call attention to the fact that the criteria for the diagnosis of nodal bradycardia are variable and often uncertain. An investigation was therefore made which involved electrocardiographic studies on dogs in which surgical ablation of the sinus node had been performed. Two of the dogs were observed over a period of three to four years.

Variation of the P-R interval with wandering pacemaker occurred only in the first months after operation and could be caused to disappear by the injection of atropine. The phenomenon is regarded as an effect of vagal tonus and in that respect is comparable to sinus arrhythmia. Polymorphism of the P waves, however, was more or less constant and could not be abolished by atropine.

There occur occasionally in cases of pure nodal rhythm, blockage of the P waves and atypical ventricular complexes which are not premature and therefore suggest ventricular escape. Physiologic vagal tonus appears responsible for these anomalies. It seems indeed to exert a much more marked effect on nodal rhythm than it does on sinus rhythm. A more unusual occurrence is sudden doubling of the rate or an abrupt lengthy pause which

is suggestive of sinoauricular block in sinus rhythm. In the absence of any more precise explanation of its cause, this type of block may be regarded as a peculiarity of both the sinoauricular and auriculoventricular nodes.

LAPLACE.

Raynaud, R.: Hypertensive Accidents Following the Injection of Acetylcholine. Arch. d. mal. du cœur. 38: 217 (Sept.-Oct.) 1945.

The injection of acetylcholine has been found to occasionally produce transient hypertension. An instance of this reaction is reported in the case of a woman 63 years old. The patient had sustained a sudden left hemiplegia. A half hour later, the author administered an injection of 0.20 Gm. of acetylcholine. Within twenty minutes, the blood pressure increased from 140/80 to 220/120, and the patient had an attack of acute pulmonary edema. Venesection, sedation, and the intravenous administration of ouabain were followed by recovery and return of the blood pressure to its previous level.

The acetylcholine which was used in this case had been in the possession of the author for seven years. It is pointed out that although the characteristic action of acetylcholine is to lower the blood pressure, the drug may cause marked hypertension when it is no longer fresh. It is possible that acetylcholine may also elevate the blood pressure when given following the administration of atropine. The author has been unsuccessful, however, in eliciting this reaction in normal subjects. He emphasizes the danger involved in using old solutions of acetylcholine, deterioration of which was undoubtedly the cause of the serious complication encountered in his patient.

LAPLACE.

Berconsky, I., and Newman, J.: Mitral Stenosis and Arterial Hypertension. Rev. argent. de cardiología. 12: 94 (May-June) 1946.

In view of existing divergence of opinion regarding the significance of the co-existence of mitral stenosis and arterial hypertension, a study was made of 150 patients, 74 with mitral stenosis and 76 with mitral disease.

Arterial hypertension as indicated by a blood pressure of 150/90 or higher was present in 28 per cent of the total group. Its incidence among women was twice that encountered among men. In patients over 40 years of age the incidence of hypertension was 50 per cent. The association of mitral stenosis and hypertension appeared about twice as frequently among Jewish patients as compared with non-Jewish patients.

It is concluded from this study that arterial hypertension has the same incidence among patients who have mitral disease as occurs in the general population, and that the association therefore does not depend upon factors peculiar to the valvular disease.

LAPLACE.

Cohen, S. M.: The Surgical Management of Peripheral Vascular Disorders. Post-Grad. M. J. 22: 1 (Jan.) 1946.

This is a review of surgical procedures used in the treatment of spastic and organic arterial diseases, costoclavicular compression thrombosis, erythromelalgia, and posttraumatic painful states. Diagnostic methods used in the study of patients with peripheral vascular diseases are discussed. The usefulness of sympathectomy in the various disorders is evaluated.

NAIDE.

Cohen, S. M.: The Surgical Management of Peripheral Vascular Disorders. II. Vascular Trauma. Post-Grad. M. J. 22: 50 (Feb.) 1946.

This is a review of advances and trends in the treatment of vascular injuries. General rules regarding ligation following arterial injury are outlined. The management of the consequences of arterial contusion is described. The author reviews and describes his own approach to the management of traumatic arterial spasm, Volkmann's contracture, vascular repair and vein grafting, false aneurysm, and arteriovenous fistula. The management of the ischemic extremity in a patient who has suffered a vascular injury is outlined.

NAIDE.

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INDEX TO VOLUME 31

AUTHORS INDEX

A

- Ashman, Richard. (*See* LaDue and Ashman), 685
 Askey, John Martin. Hemiplegia following carotid sinus stimulation, 131

B

- Baggenstoss, Archie H. (*See* Keith, Pruitt, and Baggenstoss), 527
 Batterman, Robert C., DeGraff, Arthur C., and Shorr, Harold M. Further observations on the use of mercupurin administered orally, 431
 Bayley, Robert H. The electrocardiographic effects of injury at the endocardial surface of the left ventricle, 677
 Bell, John W. (*See* York and Bell), 780
 Bernstein, Arthur. (*See* Parsonnet, Bernstein, and Klosk), 769
 —. (*See* Parsonnet, Bernstein, and Martland), 438
 —. (*See* Parsonnet, Miller, Bernstein, and Klosk), 74
 Bertacchi, Silvio. (*See* Pazzanese and Bertacchi), 33
 Bidder, Thomas G. (*See* Kline and Bidder), 254
 Blevins, Anne. (*See* Mac Neal, Blevins, and Duryee), 668
 —, and Mac Neal, Ward J. Actinomyces septicus from human endocarditis, 663
 Bodlander, Jerome W. The Wolff-Parkinson-White syndrome in association with congenital heart disease: coarctation of the aorta, 785
 Brannon, E. S. (*See* Merrill, Warren, Stead, and Brannon), 413
 —, Stead, E. A., Jr., Warren, J. V., and Merrill, A. J. Hemodynamics of acute hemorrhage in man, 407
 —. (*See* Warren, Brannon, Stead, and Merrill), 418
 Brindley, Paul. (*See* Decherd, Ruskin, and Brindley), 352
 Brown, Halla. (*See* Stewart, Evans, Haskell, and Brown), 617, 728
 Brown, W. O. Myxoma of heart, 373
 Budnitz, Joseph. (*See* Freed and Budnitz), 369
 Burch, George E. (*See* Winsor and Burch), 387

C

- Carr, David T., and Essex, Hiram E. Certain effects of positive pressure respiration on the circulatory and respiratory systems, 53
 Cole, Julia. (*See* Paul, Rhombert, and Cole), 138
 Cunningham, Robert S. Differences in blood pressure values determined by inflating and deflating the cuff of the sphygmomanometer, 220

D

- Dathe, Richard A., and Nathan, David A. Electrocardiographic changes resulting from phosphorus poisoning, 98
 —. (*See* Nathan and Dathe), 115
 Decherd, George M., Jr., Ruskin, Arthur, and Brindley, Paul. Interatrial and sinoatrial block, with an illustrative case, 352
 DeGraff, Arthur C. (*See* Batterman, DeGraff, and Shorr), 431
 Dehn, Helmut, Feil, Harold, and Rinderknecht, Robert E. Electrocardiographic changes in cases of infectious hepatitis, 183
 Drapiewski, John F. (*See* Medalia and Drapiewski), 103
 Durgin, Bernice. (*See* Zimmerman and Durgin), 93
 Duryee, A. Wilbur. (*See* Mac Neal, Blevins, and Duryee), 668

E

- Edelstein, Joseph M. Primary, massive calcification with ossification of the myocardium, 496
 Eichert, Herbert. Transient bundle branch block associated with tachycardia, 511
 Essex, Hiram E. (*See* Carr and Essex), 53
 Ethridge, Clayton B. (*See* Manchester and Ethridge), 633
 Evans, Willis F. (*See* Stewart, Evans, and Haskell), 343
 —. (*See* Stewart, Evans, Haskell, and Brown), 617, 728

F

- Fauteux, Mercier. Treatment of coronary disease with angina by pericoronary neurectomy combined with ligation of the great cardiac vein, 260
- Feil, Harold. (*See* Dehn, Feil, and Rinderknecht), 183
- Felknor, George E., and Pullen; Roseoe L. Mumps myocarditis, 238
- Fertman, M. H., and Wolff, Louis. Calcification of the mitral valve, 580
- Flynn, Joseph E., and Mann, Frank D. The presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of the thebesian veins in cardiac failure from causes other than myocardial infarction, 757
- Fox, J. Robert. (*See* Herbut and Fox), 490
- Freed, Alexander N., and Budnitz, Joseph. Pure congenital pulmonary stenosis, 369
- Freundlich, J. Paroxysmal ventricular tachycardia, 557

G

- Gilbert, N. C. (*See* Kyser, Ginsberg, and Gilbert), 451
- Ginsberg, Harold. (*See* Kyser, Ginsberg, and Gilbert), 451
- Glenn, Paul M., and Read, Hilton S. A case report of similar symptom produced by hyperactive carotid sinus reflex, angina pectoris, and myocardial infarction, 792
- Goetz, Robert H. The rate and control of the blood flow through the skin of the lower extremities, 146

H

- Haskell, Helen S. (*See* Stewart, Evans and Haskell), 343
- (*See* Stewart, Evans, Haskell, and Brown), 617, 728
- Herbut, Peter A., and Fox, J. Robert. Persistent right aortic arch with atresia of the entire main pulmonary artery, 490
- Hollander, George. Electrocardiographic changes in scrub typhus fever, 481
- Howard, Frederick H. A method for the construction of the vectorcardiogram from the Einthoven electrocardiogram, 191
- A method for the orthodiagraphic measurement of the transverse diameter of the heart by means of the simple fluoroscope, 724
- Hussey, Hugh Hudson, Katz, Sol, and Yater. Wallace M. The superior vena caval syndrome; report of thirty-five cases, 1

K

- Katz, L. N. (*See* Malinow, Katz, and Kondo), 702
- Katz, Sol. (*See* Hussey, Katz, and Yater), 1
- Kay, Calvin F., and Livingood, Clarence S. Myocardial complications of cutaneous diphtheria, 744
- Keith, Norman M., Pruitt, Raymond D., and Baggenstoss, Archie H. Electrocardiographic changes in pericarditis associated with uremia, 527
- Kline, Edward M., and Bidder, Thomas G. A study of the subjective sensations associated with extrasystoles, 254
- Klosk, Emanuel. (*See* Parsonnet, Bernstein, and Klosk), 769
- (*See* Parsonnet, Miller, Bernstein, and Klosk), 74
- Knighton, James E. (*See* Palatucci and Knighton), 364
- Kondo, B. (*See* Malinow, Katz, and Kondo), 702
- Kyser, Franklin A., Ginsberg, Harold, and Gilbert, N. C. The effect of certain drugs upon the cardiotoxic lesions of digitalis in the dog, 451

L

- LaDue, John S., and Ashman, Richard. Electrocardiographic changes in acute glomerulonephritis, 685
- Levine, Harold D. Pathologic study of thirty-one cases of scrub typhus fever with especial reference to the cardiovascular system, 314
- Livingood, Clarence S. (*See* Kay and Livingood), 744
- Logue, Robert Bruce. (*See* Wallace and Logue), 223
- (*See* Wendkos and Logue), 711
- Luisada, Aldo A., and Sarnoff, Stanley J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. I. Effect of intra-arterial and intravenous infusions, 270
- and —. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. II. Mechanical and neurogenic elements, 282
- and —. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. III. Pharmacologic experiments, 293

M

- McDonald, Roger K. The coincidence of auricular fibrillation and bacterial endocarditis, 308
- Macht, David I. Thromboplastic properties of some mercurial diuretics, 460

- Mac Neal, Ward J., Blevins, Anne, and Duryee, A. Wilbur. Clinical arrest of endocardial actinomycosis after forty-four million units of penicillin, 668
- , (See Blevins and Mac Neal), 663
- Malinow, M. R., Katz, L. N., and Kondo, B. Is there a vagal pulmonocoronary reflex in pulmonary embolism? 702
- Manchester, Benjamin, and Ethridge, Clayton B. An evaluation of the use of multiple versus single preordial leads, in conjunction with the three limb leads, for practical clinical electrocardiography, 633
- Mann, Frank D. (See Flynn and Mann), 757
- Martland, Harrison S. (See Parsonnet, Bernstein, and Martland), 438
- Medalia, Leon S., and Drapiewski, John F. Congenital defect of the aortic vestibule complicated by bacterial endocarditis with perforation and death from cardiac tamponade, 103
- Merrill, A. J. (See Brannon, Stead, Warren, and Merrill), 407
- , (See Warren, Brannon, Stead, and Merrill), 418
- , Warren, J. V., Stead, E. A., Jr., and Brannon, E. S. The circulation in penetrating wounds of the chest: a study by the method of right heart catheterization, 413
- Meyers, Lawrence, and Poindexter, Charles A. A study of the prothrombin time in normal subjects and in patients with arteriosclerosis, 27
- Miller, Ralph. (See Parsonnet, Miller, Bernstein, and Klosk), 74
- , and Perelman, Julius S. Multiple disturbances of rhythm and conduction and unusual auricular T wave in a case of myocardial infarction, 501
- Monroe, Willys M. Subacute bacterial endocarditis successfully treated with penicillin, 651
- N
- Nathan, David A., and Dathe, Richard A. Pericarditis with effusion following infections of the upper respiratory tract, 115
- , (See Dathe and Nathan), 98
- P
- Palatucci, Oscar A., and Knighton, James E. Spontaneous mediastinal emphysema, 364
- Parsonnet, Aaron E., Bernstein, Arthur, and Klosk, Emanuel. Ventricular fibrillation, 769
- , Bernstein, Arthur, and Martland, Harrison, S. Massive left auricle with special reference to its etiology and mechanism, 438
- , Miller, Ralph, Bernstein, Arthur, and Klosk, Emanuel. Bigeminy, 74
- Paul, W. D., Rhomberg, C., and Cole, Julia. Transitory A-V block occurring during scarlet fever, 138
- Pazzanese, Dante, and Bertacchi, Silvio. Normal electrocardiograms in cardiovascular disease, 33
- Perelman, Julius S. (See Miller and Perelman), 501
- Poindexter, Charles A. (See Meyers and Poindexter), 27
- Pruitt, Raymond D. (See Keith, Pruitt, and Baggenstoss), 527
- Pullen, Roscoe L. (See Felknor and Pullen), 238
- R
- Read, Hilton S. (See Glenn and Read), 792
- Reichsman, Francis. Studies on pathogenesis of pulmonary edema following bilateral vagotomy, 590
- Rhomberg, C. (See Paul, Rhomberg, and Cole), 138
- Rinderknecht, Robert E. (See Dehn, Feil, and Rinderknecht), 183
- Ruskin, Arthur. (See Decherd, Ruskin, and Brindley), 352
- Rutstein, David D. (See Thomson, Rutstein, Tolmack, and Walker), 565
- S
- Sarnoff, Stanley J. (See Luisada and Sarnoff), 270, 282, 293
- Schlamowitz, Isadore. An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. I. The duration of the Q-T interval and its relationship to the cycle length (R-R interval), 329
- , An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. II. The duration of the T-P interval and its relationship to the cycle length (R-R interval), 464
- , An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. III. The duration of the P-R interval and its relationships to the cycle length (R-R interval), 473
- Shorr, Harold M. (See Batterman, DeGraff, and Shorr), 431
- Sprague, Howard B. The effects of malaria on the heart, 426
- Stead, E. A., Jr. (See Brannon, Stead, Warren, and Merrill), 407
- , (See Merrill, Warren, Stead, and Brannon), 413

- , (See Warren, Brannon, Stead, and Merrill), 418
- Stein, Irwin. The effects of change of position of the arm upon blood pressure, 477
- Stewart, Harold J., Evans, Willis F., and Haskell, Helen S. The peripheral blood flow under basal conditions in older male subjects with normal and elevated blood pressures, 343
- , —, —, and Brown, Halla. The effect of splanchnic resection on the peripheral blood flow and rectal and skin temperatures in hypertension, 728
- , —, —, and —. The peripheral blood flow and rectal and skin temperatures in hypertension, 617

T

- Thomson, K. Jefferson, Rutstein, David D., Tolmack, Daniel M., and Walker, William H. Electrocardiographic studies during and after pneumococcus pneumonia, 565
- Tolmack, Daniel M. (See Thomson, Rutstein, Tolmack, and Walker), 565

W

- Walker, William H. (See Thomson, Rutstein, Tolmack, and Walker), 565
- Wallace, Joseph J., and Logue, Robert Bruce. Metastatic carcinoma as a cause of constrictive pericarditis, 223
- Ward, Lawrence S. Abnormal electrocardiogram following recovery from paroxysmal tachycardia, 645

- Warren, J. V., Brannon, E. S., Stead, E. A., Jr., and Merrill, A. J. Pericardial tamponade from stab wound of the heart and pericardial effusion or empyema: a study utilizing the method of right heart catheterization, 418
- , (See Brannon, Stead, Warren, and Merrill), 407
- , (See Merrill, Warren, Stead, and Brannon), 413
- Wendkos, Martin H., and Logue, Robert Bruce. Unstable T waves in Leads II and III in persons with neurocirculatory asthenia, 711
- Winsor, Travis, and Burch, George E. Use of the phlebomanometer; normal venous pressure values and a study of certain clinical aspects of venous hypertension in man, 387
- Wolff, Louis. (See Fertman and Wolff), 580

Y

- Yater, Wallace M. (See Hussey, Katz, and Yater), 1
- York, J. S., and Bell, John W. Fatal coronary failure without infarction: report of a case, 780

Z

- Ziegler, Robert F. The cure of subacute bacterial endarteritis by surgical ligation in a patient with patent ductus arteriosus complicated by the presence of multiple congenital cardiac defects, 231
- Zimmerman, Joseph J., and Durgin, Bernice. Staphylococcus aureus septicemia and pericarditis treated with penicillin, 93

SUBJECT INDEX*

A

- Abscess, brain, with congenital heart disease, 384*
- Acetylcholine and epinephrine, action of, on turtle ventricle, 381*
- effect of, on atropinized denervated heart, 382*
- hypertensive accidents following injection of, 805*
- Aetionomyces septicus from human endocarditis (Blevins and Mac Neal), 663
- Aetionomycosis, endocardial, clinical arrest of, after forty-four million units of penicillin (Mac Neal et al.), 663
- Activity, physical, early, in rheumatic fever, therapeutic value of, preliminary report, 384*
- Adenomas, small, of adrenal cortex in hypertension and diabetes, 520
- Anastomosis, observations relating to cardiac hypertrophy produced in rabbit by arteriovenous anastomosis, effect of closure of, 243*
- Anesthesia, ether, bilateral cervical vagotomy and sympathectomy in rat under (Reichsman), 595
- urethane, bilateral cervical vagotomy under (Reichsman), 599
- Angina pectoris and tobacco, 525*
- hyperactive carotid sinus reflex, and myocardial infarction, case report of similar symptoms produced by (Glenn and Read), 792
- paravertebral block and electrocardiogram in, 802*
- treatment of coronary disease with, by pericoronary neurectomy combined with ligation of great cardiac vein (Fauteux), 260
- Anginal syndrome, treatment of, with thiouracil, 247*
- Announcement, 113
- Aorta, coarctation and acute dissection of, associated with pregnancy, 247*
- congenital, and its surgical treatment, 381*
- surgical correction for, 380*
- Wolff-Parkinson-White syndrome in association with congenital heart disease (Bodlander), 785
- Aortic arch, persistent right, with atresia of entire main pulmonary artery (Herbut and Fox), 490
- insufficiency, changes in coronary circulation in course of, in young subjects, 804*
- vestibule, congenital defect of, complicated by bacterial endocarditis with perforation and death from cardiac tamponade (Medalia and Drapiewski), 103

- Arm, effect of change of position of, upon blood pressure (Stein), 477
- Arrhythmia, sinus, on cause of respiratory variation of ballistocardiogram, with note on, 659
- Arterial pressure, pulmonary, in dogs, measurement of, 107*
- Arteriosclerosis, experimental; VIII. Effect of feeding olive oil on absorption and deposition of cholesterol, 381*
- study of prothrombin time in normal subjects and in patients with (Meyers and Poindexter), 27
- Arteriovenous anastomosis, effect of closure of anastomosis, observations relating to cardiac hypertrophy produced in rabbit by, 243*
- Artery, pulmonary, contribution to study of congenital dilatation of, 656
- entire main, persistent right aortic arch with atresia of (Herbut and Fox), 590
- Arthritis, rheumatoid, characteristic vascular pattern in patients with, 380*
- Asthenia, neurocirculatory, unstable T waves in Leads II and III in persons with (Wendkos and Logue), 711
- Atresia of entire main pulmonary artery, persistent right aortic arch with (Herbut and Fox), 490
- Atropinized denervated heart, effect of acetylcholine on, 382*
- Auricle, massive left, with special reference to its etiology and mechanism (Parsonnet et al.), 438
- Auricular fibrillation and bacterial endocarditis, coincidence of (McDonald), 308
- functional paroxysmal, 800*
- heart sounds, recognition and clinical significance of, 659*
- T wave, unusual, multiple disturbances of rhythm and conduction and, in case of myocardial infarction (Miller and Perelman), 501
- Auriculoventricular dissociation, flutter and, in patient with myopathy, 804*
- Auscultation, intrathoracic, in pneumothorax, 800*
- A-V block, transitory, occurring during scarlet fever (Paul et al.), 138

B

- Bacterial endarteritis, subacute, cure of, by surgical ligation in patient with patent ductus arteriosus complicated by presence of multiple congenital cardiac defects (Ziegler), 231
- endocarditis, coincidence of auricular fibrillation and (McDonald), 308

An asterisk () after a page number indicates the reference is an abstract and not an original article.

Bacterial endocarditis—Cont'd

- ineffectiveness of penicillin in some cases of, 380*
- subacute, penicillin treatment of, 384*
- Streptococcus s. b. e.* in, 383*
- treated with penicillin (Monroe), 651
- with perforation and death from cardiac tamponade, congenital defect of aortic vestibule complicated by (Medalia and Drapiewski), 103

Ballistocardiogram, on cause of respiratory variation of, with note on sinus arrhythmia, 659*

Basal conditions, peripheral blood flow under, in older male subjects with normal and elevated blood pressures (Stewart et al.), 343

Bigeminal rhythm, persistent ventricular, in apparently normal hearts, 659*
rhythms, electrocardiographic (Parsonnet et al.), 75

Bigeminy (Parsonnet et al.), 74

Block, bundle branch, transient, associated with tachycardia (Eichert), 511
interatrial and sinoatrial, with illustrative case (Decherd et al.), 352

Blood flow, cerebral, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men, effects of active and passive hyperventilation of, 801*

effect of body heating on (Goetz), 162
in peripheral vascular diseases (Goetz), 173

in sympathectomized extremities (Goetz), 168

peripheral, and rectal and skin temperatures in hypertension (Stewart et al.), 617

and rectal and skin temperatures in hypertension, effect of splanchnic resection on (Stewart et al.), 728

under basal conditions in older male subjects with normal and elevated blood pressures (Stewart et al.), 343

rate of, in toes (Goetz), 158

through skin of lower extremities, rate and control of (Goetz), 146

pressure and serum thiocyanate, relation of, 385*

cerebral blood flow, cerebral oxygen consumption, cardiac output and effects of active and passive hyperventilation of, 801*

effect of change of position of arm upon (Stein), 477

in hypertension, range of, 383*

of patients with hypertension and far-advanced renal disease, effect of high spinal anesthesia on—its possible relationship to pathogenesis of hypertension (V); studies in hypertension, 379*

Blood pressure—Cont'd

pulse rate and, in infancy and early childhood, 378*

values determined by inflating and deflating cuff of sphygmomanometer (Cunningham), 220

pressures, normal and elevated, peripheral blood flow under basal conditions in older male subjects with (Stewart et al.), 343

transfusion, intracardiac, 385*

volume determination, plasma and, in bilaterally vagotomized rats (Reichsman), 605

Body heating, effect of, on blood flow (Goetz), 162

Book reviews, 251, 661

Brain abscess with congenital heart disease, 384*

and heart, combined acute vascular lesions of, clinical-pathologic study of fifteen cases, 248*

Buerger's disease, 654*

Bundle branch block, transient, associated with tachycardia (Eichert), 511

Burn shock, nature of circulatory changes in, 524*

C

Calcification of mitral valve (Fertman and Wolff), 580

primary, massive, with ossification of myocardium (Edelstein), 496

Carcinoma, metastatic, as cause of constrictive pericarditis (Wallace and Logue), 223

Cardiac complications in infectious mononucleosis, electrographic evidence of, 655*

cycle in electrocardiograms of normal men, analysis of time relationships within (Schlamowitz), 329, 464, 473

damage, residual, question of, in scrub typhus (Levine), 326

defects, multiple congenital, cure of subacute bacterial endarteritis by surgical ligation in patient with patent ductus arteriosus complicated by presence of (Ziegler), 231

drive, venous return in absence of, 382*

dysfunction, relation of nutritional deficiency to, 525*

failure from causes other than myocardial infarction, presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins in (Flynn and Mann), 757

injury potential, development and contour of, 525*

Cardiac—Cont'd

- output, cerebral blood flow, cerebral oxygen consumption, and blood pressure of normal young men, effects of active and passive hyperventilation of, 801⁺
- in man, study of some of errors of right heart catheterization, 654⁺
- reaction to right and left pneumothorax, considerations of, 524⁺
- tamponade, congenital defect of aortic vestibule complicated by bacterial endocarditis with perforation and death from (Medalia and Drapiewski), 103
- vein, great, treatment of coronary disease with angina by pericoronary neurectomy combined with ligation of (Fauteux), 260
- Cardioinhibitory vagus endings in dog, blocking action of cinchona alkaloids and certain related compounds on, 242⁺
- Cardio-pulmonary function during pregnancy, 251 (B. Rev.)
- Cardiotoxic lesions of digitalis in dog, effect of certain drugs upon (Kyser et al.), 451
- Cardiovascular defects, congenital, physiopathology and surgical treatment of, 519⁺
- disease, normal electrocardiograms in (Pazzanese and Bertacchi), 33
- disturbances in tsutsugamushi disease, 248⁺
- receptors, paroxysmal pulmonary edema consequent to stimulation of; I. Effect of intra-arterial and intravenous infusions (Luisada and Sarnoff), 270
- II. Mechanical and neurogenic elements (Luisada and Sarnoff), 282
- III. Pharmacologic experiments (Luisada and Sarnoff), 293
- system, gout and its effect on, 111⁺
- pathologic study of thirty-one cases of scrub typhus fever with especial reference to (Levine), 314
- Carotid shudder, 379⁺
- sinus, hyperactive, reflex, angina pectoris, and myocardial infarction. case report of similar symptoms produced by (Glenn and Read), 792
- stimulation, hemiplegia following (Askey), 131
- other cerebral disturbances following (Askey), 135
- Catheterization, right heart, study by method of; circulation in penetrating wounds of chest (Merrill et al.), 413
- study of some of errors in method of: cardiac output in man, 654⁺

Catheterization, right heart—Cont'd

- study utilizing method of; pericardial tamponade from stab wound of heart and pericardial effusion or empyema (Warren et al.), 418
- Cervical vagotomy, bilateral, and sympathectomy in rat under ether anesthesia (Reichsman), 595
- under urethane anesthesia (Reichsman), 599
- left, right thoracic and (Reichsman), 600
- Chest, circulation in penetrating wounds of; study by method of right heart catheterization (Merrill et al.), 413
- leads, configuration of epicardial and endocardial extrasystoles in, 655⁺
- Childhood, early, infancy and, pulse rate and blood pressure in, 378⁺
- precordial leads in; comment on presence of double upward deflections in leads from sternal region of normal children, 657⁺
- Children, Denver school, prevalence of rheumatic heart disease in, 250⁺
- prevention of rheumatic recurrences in, by use of sulfathiazole and sulfadiazine, 379⁺
- Cholesterol, effect of feeding olive oil on absorption and deposition of (VIII); experimental arteriosclerosis, 381⁺
- Cinchona alkaloids and certain related compounds, blocking action of, on cardioinhibitory vagus endings in dog, 242⁺
- Circulation, effects of malaria on (Sprague), 427
- failure in hunger edema, 383⁺
- in constrictive pericarditis, induced changes in, 803⁺
- in experimental neurogenic hypertension, 110⁺
- in penetrating wounds of chest; study by method of right heart catheterization (Merrill et al.), 413
- lying and standing, of tremor, and of program of bed exercises and early rising, studies of (I); convalescence of surgical procedures, 249⁺
- Circulatory and respiratory systems, certain effects of positive pressure respiration on (Carr and Essex), 53
- changes in burn shock, nature of, 524⁺
- Coarctation and acute dissection of aorta associated with pregnancy, 247⁺
- congenital, of aorta and its surgical treatment, 381⁺
- of aorta; experimental studies regarding its surgical correction, 112⁺
- surgical correction for, 380⁺
- Wolff-Parkinson-White syndrome in association with congenital heart disease (Bodlander), 785

- Cold, heat and, action of, on electrogram of cardiac ventricle, 107*
- Conduction, multiple disturbances of rhythm and, unusual auricular T wave in case of myocardial infarction (Miller and Perelman), 501
- Congenital defect of aortic vestibule complicated by bacterial endocarditis with perforation and death from cardiac tamponade (Medalia and Drapiewski), 103
- heart disease, Wolff-Parkinson-White syndrome in association with: coarctation of aorta (Bodlander), 785
- Congestive heart failure, right ventricular, venous pressure in patients with (Winsor and Burch), 397
- Constrictive pericarditis, metastatic carcinoma as cause of (Wallace and Logue), 223
- Construction of vectorcardiogram from Einthoven electrocardiogram, method for (Howard), 191
- Control, rate and, of blood flow through skin of lower extremities (Goetz), 146
- Cor pulmonale, chronic, 522*
- Coronary artery disease among physicians, 243*
- circulation, changes in, in course of aortic insufficiency in young subjects, 804*
- disease, hypoxemia tests in, 802*
- with angina, treatment of, by pericoronary neurectomy, combined with ligation of great cardiac vein (Fautoux), 260
- failure, fatal, without infarction: report of case (York and Bell), 780
- thrombosis, acute, dicumarol in, 522*
- Cuff or sphygmomanometer, differences in blood pressure values determined by inflating and deflating (Cunningham), 220
- Curacao, Netherlands West Indies, occurrence of rheumatic carditis in native population of, 658*
- Cutaneous diphtheria, myocardial complications of (Kay and Livingood), 744
- Cycle, cardiac, in electrocardiograms of normal men, analysis of time relationships within (Schlamowitz), 329, 464, 473
- length (R-R interval), duration of P-R interval and its relationship to (Schlamowitz), 473
- duration of Q-T interval and its relationship to (Schlamowitz), 329
- duration of T-P interval and its relationship to (Schlamowitz), 464
- D
- Death following intravenous administration of papaverine hydrochloride, 243*
- perforation and, from cardiac tamponade, congenital defect of aortic vestibule complicated by bacterial endocarditis with (Medalia and Drapiewski), 103
- Death—Cont'd
- bule complicated by bacterial endocarditis with (Medalia and Drapiewski), 103
- Defect, congenital, of aortic vestibule complicated by bacterial endocarditis with perforation and death from cardiac tamponade (Medalia and Drapiewski), 103
- Defects, congenital, following maternal rubella, 656*
- multiple congenital cardiac, cure of subacute bacterial endarteritis by surgical ligation in a patient with patent ductus arteriosus complicated by presence of (Ziegler), 231
- Degeneration, endocardial and subendocardial, mural thrombi, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Dehydration, salt depletion and, hemodynamic changes in, 660*
- Denver school children, prevalence of rheumatic heart disease in, 250*
- Diabetes, hypertension and, small adenomas of adrenal cortex in, 520*
- Diameter, transverse, of heart, method for orthodiagraphic measurement of, by means of simple fluoroscope (Howard), 724
- Dicumarol in acute coronary thrombosis, 522*
- Digitalis, effect of certain drugs upon cardiotoxic lesions of, in dog (Kyser et al.), 451
- Dilatation, congenital, of pulmonary artery, contribution to study of, 656*
- Diphtheria, cutaneous, myocardial complications of (Kay and Livingood), 744
- Dissection, acute, coarctation and, of aorta associated with pregnancy, 247*
- Disturbances, multiple, of rhythm and conduction and unusual auricular T wave in case of myocardial infarction (Miller and Perelman), 501
- Diuretics, mercurial; intolerance as shown by skin sensitivity, 378*
- thromboplastic properties of some (Macht), 460
- Drugs, certain, effect of, upon cardiotoxic lesions of digitalis in dog (Kyser et al.), 451
- Ductus arteriosus, patent, complicated by presence of multiple congenital cardiac defects, cure of subacute bacterial endarteritis by ligation in patient with (Ziegler), 231
- Dystrophy, progressive muscular, changes in musculature of gastrointestinal tract and in myocardium in, 242*

E

- Edema, hunger, circulation failure in, 383⁻
 paroxysmal pulmonary, consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270, 282, 293
 pulmonary, following bilateral vagotomy, studies on pathogenesis of (Reichsman), 590
 general considerations on mechanism of (Luisada and Sarnoff), 303
- Effusion, pericardial, or empyema, pericardial tamponade from stab wound of heart and; study utilizing method of right heart catheterization (Warren et al.), 418
 pericarditis with, following infections of upper respiratory tract (Nathan and Dathe), 115
- Einthoven electrocardiogram, method for construction of vectorecardiogram from (Howard), 191
- Ejection, cardiac, action of, on venous return, 655⁻
- Electrocardiogram, abnormal, following recovery from paroxysmal tachycardia (Ward), 645
 abnormalities in, following hemolytic streptococcus sore throat, 658⁻
- Einthoven, method for construction of vectorecardiogram from (Howard), 191
 paravertebral block and, in angina pectoris, 802⁺
 prognostic value of, 661 (B. Rev.)
- Electrocardiograma, valor pronostico del, 661 (B. Rev.)
- Electrocardiograms in traumatic shock in man, 244^{*}
 normal, in cardiovascular disease (Pazzanese and Bertacchi), 33
 of normal men, analysis of time relationships with cardiac cycle in; I. Duration of Q-T interval and its relationship to cycle length (R-R interval) (Schlamowitz), 329
 II. Duration of T-P interval and its relationship to cycle length (R-R interval) (Schlamowitz), 464
 III. Duration of P-R interval and its relationship to cycle length (R-R interval) (Schlamowitz), 473
- Electrocardiographic bigeminal rhythms (Parsonnet et al.), 75
 changes following heat stroke, 383⁺
 in acute glomerulonephritis (LaDue and Ashman), 685
 in cases of infectious hepatitis (Dehn et al.), 183
 in pericarditis associated with uremia (Keith et al.), 527
 in scrub typhus fever (Hollander), 481
 resulting from phosphorus poisoning (Dathe and Nathan), 98

Electrocardiographic—Cont'd

- effects of injury at endocardial surface of left ventricle (Bayley), 677
 studies during and after pneumococcus pneumonia (Thomson et al.), 565
- Electrocardiography, practical clinical, evaluation of use of multiple versus single precordial leads in conjunction with three limb leads for (Manchester and Ethridge), 633
- Electrogram of cardiac ventricle, action of heat and cold on different components of, 107⁺
- Emboli in retinal arteries, clinical differentiation of, from endarteritis, 245⁻
- Embolism, pulmonary, is there vagal pulmonocoronary reflex in? (Malinow et al.), 702
 ligation of inferior vena cava for prevention of, 243⁺
- Emetine, effects of, on heart, 379⁺
- Emphysema, pulmonary, following prolonged positive pressure respiration (Carr and Essex), 68
 spontaneous mediastinal (Palatucci and Knighton), 364
- Empyema, pericardial effusion or, pericardial tamponade from stab wound of heart and; study utilizing method of right heart catheterization (Warren et al.), 418
- Encephalitis, meningo, rheumatic heart disease associated with, 113⁺
- Endarteritis, clinical differentiation of emboli in retinal arteries from, 245⁻
- Endocardial actinomycosis, clinical arrest of, after forty-four million units of penicillin (Mac Neal et al.), 668
 and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
 surface of left ventricle, electrocardiographic effects of injury at (Bayley), 677
- Endocarditis, bacterial, coincidence of auricular fibrillation and (McDonald), 308
 ineffectiveness of penicillin in some cases of, 380⁺
 with perforation and death from cardiac tamponade, congenital defect of aortic vestibule complicated by (Medalia and Drapiewski), 103
 enterococcal, clinical arrest in, 382⁻
 experimental, rheumatic-like and bacterial in rats, 111⁺
 human, Actinomyces septicus from (Blevins and Mac Neal), 663
 subacute bacterial, penicillin treatment of, 384⁻, (Monroe), 651, 658⁻
 Streptococcus s.b.e. in, 383⁺

Enterococcal endocarditis, clinical arrest in, 382*

Epinephrine, acetylcholine and, action of, on turtle ventricle, 381*

Esophago-cardiogram, 800*

Ether anesthesia, bilateral cervical vagotomy and sympathectomy in rat under (Reichsman), 595

Etiology and mechanism, massive left auricle with special reference to (Parsonnet et al.), 438

Exercise, bed, and early rising, studies of circulation lying and standing, of tremor, and of (I); convalescence from surgical procedures, 249*

effect of, on size and shape of T wave (Dehn et al.), 188

step-up, on benches of different heights, pulse reaction to performing, 654*

test, mild, studies of various physiological responses to (II); convalescence from surgical procedures, 249*

Experiments, pharmacologic (III); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 293

Extrasystoles, epicardial and endocardial, configuration of, in chest leads, 655*

study of subjective sensations associated with (Kline and Bidder), 254

Extremities, lower, rate and control of blood flow through skin of (Goetz), 146

venous pressures in disorders of venous system of, 380*

sympathectomized, blood flow in (Goetz), 168

F

Fibrillation, auricular, and bacterial endocarditis, coincidence of (McDonald), 308

functional paroxysmal auricular, 800*

ventricular (Parsonnet et al.), 769

Fluoroscope, simple, method for orthodiagraphic measurement of transverse diameter of heart by means of (Howard), 724

Flutter and auriculoventricular dissociation in patient with myopathy, 804*

Frostbite, human, experimental subcutaneous heparin in Pitkin menstruum for treatment of, 799*

G

Gastrointestinal tract, changes in musculature of, and in myocardium in progressive muscular dystrophy, 242*

Glomerulonephritis, acute, electrocardiographic changes in (LaDue and Ashman), 685

Gout and its effect on cardiovascular system, 111*

H

Harveian oration on rheumatic fever and rheumatic heart disease, 246*

Headache, typical, of essential hypertension; etiological considerations and report of new form of therapy, 250*

Heart and other organs, pathologic changes in, in scrub typhus fever (Levine), 315

atropinized denervated, effect of acetylcholine on, 382*

brain and combined acute vascular lesions: of, clinical-pathologic study of fifteen cases, 248*

disease, congenital, brain abscess with, 384*

Wolff-Parkinson-White syndrome in association with: coarctation of aorta (Bodlander), 785

or hypertension, re-examination of veterans discharged because of, 520*

effects of emetine on, 379*

of malaria on (Sprague), 426

failure, congestive, in scrub typhus (Levine), 325

left ventricular, insomnia due to, 385*

right ventricular congestive, venous pressure in patients with (Winsor and Burch), 397

mechanism of action of jaundice on (Dehn et al.), 187

method for orthodiagraphic measurement of transverse diameter of, by means of simple fluoroscope (Howard), 724

myxoma of (Brown), 373

right, catheterization, circulation in penetrating wounds of chest (Merrill et al.), 413

pericardial tamponade from stab wound of heart and pericardial effusion or empyema (Warren et al.), 418

sounds, auricular, recognition and clinical significance of, 659*

stab wound of, and pericardial effusion or empyema, pericardial tamponade from; study utilizing method of right heart catheterization (Warren et al.), 418

tracheobronchial tree, and inferior vena cava of normal dogs, effects of positive pressure respiration on (Carr and Essex), 61

Hearts, apparently normal, persistent ventricular bigeminal rhythm in, 659*

Heat and cold, action of, on different components of electrogram of cardiac ventricle, 107*

stroke, electrocardiographic changes following, 383*

Hemiplegia following carotid sinus stimulation (Askey), 131

Hemodynamic changes in salt depletion and in dehydration, 660*

- Hemodynamics of acute hemorrhage in man (Brannon et al.), 407
- Hemolytic streptococcus sore throat, abnormalities in electrocardiogram following, 658*
- Hemorrhage, acute, in man, hemodynamics of (Brannon et al.), 407
or trauma of limbs, effects of positive pressure respiration on circulation and respiration when combined with (Carr and Essex), 64
- Hemorrhagic phenomena in scrub typhus (Levine), 325
shock; definition and criteria for its diagnosis, 660*
- Heparin, subcutaneous, in Pitkin menstuum for treatment of experimental human frostbite, 799*
- Hepatitis, infectious, electrocardiographic changes in cases of (Dehn et al.), 183
- Hyperactive carotid sinus reflex, angina pectoris, and myocardial infarction, case report of similar symptoms produced by (Glenn and Read), 792
- Hypersensitivity and rheumatic fever, 801*
- Hypertension and diabetes, small adenomas of adrenal cortex in, 520*
arterial, critical study of medical treatment of, 523*
mitral stenosis and, 805*
production of, by chronic renal artery-nerve stimulation, 246*
surgical treatment of, 521*
effect of splanchnic resection on peripheral blood flow and rectal and skin temperatures in (Stewart et al.), 728
essential, typical headache of; etiological considerations and report of new form of therapy, 250*
experimental neurogenic, circulation in, 110*
heart disease or, re-examination of veterans discharged because of, 520*
human, treatment of, with kidney extract, 799*
peripheral blood flow and rectal and skin temperatures in (Stewart et al.), 617
range of blood pressure in, 383*
sodium restriction in diet for, 112*
studies in; V. Effect of high spinal anesthesia on blood pressure of patients with hypertension and far-advanced renal disease—its possible relationship to pathogenesis of hypertension, 379*
venous, in man, normal venous pressure values and study of certain clinical aspects of; use of phlebomanometer (Winsor and Burch), 387
- Hypertensive accidents following injection of acetylcholine, 805*
cardiovascular disease, essential, in man, experiences with surgical treatment of, 245*
- Hypertrophy, cardiac, produced in rabbit by arteriovenous anastomosis, effect of closure of anastomosis, observations relating to, 243*
- Hypoxemia tests in coronary disease, 802*
- I
- In memoriam—Fred M. Smith, 253
- Infancy and early childhood, pulse rate and blood pressure in, 378*
- Infarction, fatal coronary failure without: report of case (York and Bell), 780
myocardial, case report of similar symptoms produced by hyperactive carotid sinus reflex, angina pectoris, and (Glenn and Read), 792
multiple disturbances of rhythm and conduction and unusual auricular T wave in case of (Miller and Perelman), 501
presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins in cardiac failure from causes other than (Flynn and Mann), 757
- Infections of upper respiratory tract, pericarditis with effusion following (Nathan and Dathe), 115
- Infectious hepatitis, electrocardiographic changes in cases of (Dehn et al.), 183
- Inferior vena cava, ligation of, for prevention of pulmonary embolism, 243*
- Infusions, intra-arterial and intravenous, effect of (I); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270
- Injury at endocardial surface of left ventricle, electrocardiographic effects of (Bayley), 677
potential, cardiac, development and contour of, 525*
- Insomnia due to left ventricular heart failure, 385*
- Inspiratory and expiratory resistance, rats breathing against (Reichsman), 603
resistance, rats breathing against (Reichsman), 601
- Interatrial and sinoatrial block, with illustrative case (Decherd et al.), 352
- Intolerance as shown by skin sensitivity: mercurial diuretics, 378*
- Intra-abdominal pressure and regulation of venous return, 107*

- Intra-arterial infusions, effect of (I); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270
- Intravenous, infusions, effect of (I); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270
- J
- Jaundice, mechanism of action of, on heart (Dehn et al.), 187
- K
- Kidney extract, treatment of human hypertension with, 799*
- L
- Leads II and III, unstable T waves in, in persons with neurocirculatory asthenia (Wendkos and Logue), 711
- chest, configuration of epicardial and endocardial extrasystoles in, 655*
- precordial, in childhood; comment on presence of double upward deflections in leads from sternal region of normal children, 657*
- multiple versus single, evaluation of use of, in conjunction with three limb leads, for practical clinical electrocardiography (Manchester and Ethridge), 633
- Lesions, cardiotoxic, of digitalis in dog, effect of certain drugs upon (Kyser et al.), 451
- Letters, 377
- Ligation of great cardiac vein, treatment of coronary disease with angina by pericoronary neurectomy combined with (Fauteux), 260
- coronary vein in man (Fauteux), 261
- Limb leads, three, evaluation of use of multiple versus single precordial leads in conjunction with, for practical clinical electrocardiography (Manchester and Ethridge), 633
- Lower extremities, rate and control of blood flow through skin of (Goetz), 146
- M
- Malaria, effects of, on heart (Sprague), 426
- Maternal rubella, congenital defects following, 656*
- Mechanical and neurogenic elements (II); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 282
- Mechanism, etiology and, massive left auricle with special reference to (Parsonnet et al.), 438
- Mediastinal emphysema, spontaneous (Palatucci and Knighton), 364
- Medical treatment of arterial hypertension, critical study of, 523*
- Meningo encephalitis, rheumatic heart disease associated with, 113*
- Mereupurin administered orally, further observations on use of (Batterman et al.), 431
- Mereurial diuretics; intolerance as shown by skin sensitivity, 378*
- thromboplastic properties of some (Macht), 460
- Metastatic carcinoma as cause of constrictive pericarditis (Wallace and Logue), 223
- Method for construction of vectorcardiogram from Einthoven electrocardiogram (Howard), 191
- Mitral valve, calcification of (Fertman and Wolff), 580
- Mononucleosis, infectious, electrographic evidence of cardiac complications in, 655*
- Morgagni-Adams-Stokes syndrome, special reference to; ventricular fibrillation (Parsonnet et al.), 769
- Mumps (epidemic parotitis), acute myocarditis in, 523*
- myocarditis (Felknor and Pullen), 238
- Mural thrombi, endocardial and subendocardial degeneration, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Musculature of gastrointestinal tract, changes in, and in myocardium in progressive muscular dystrophy, 242*
- Myocardial complications of cutaneous diphtheria (Kay and Livingood), 744
- infarction, case report of similar symptoms produced by hyperactive carotid sinus reflex, angina pectoris, and (Glenn and Read), 792
- multiple disturbances of rhythm and conduction and unusual auricular T wave in case of (Miller and Perelman), 501
- presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins in cardiac failure from causes other than (Flynn and Mann), 757
- Myocarditis, acute, in mumps (epidemic parotitis), 523*
- nonspecific, 112*
- mumps (Felknor and Pullen), 238

- Myocardium, musculature of gastrointestinal tract and, changes in, in progressive muscular dystrophy, 242⁺
 primary, massive calcification with ossification of (Edelstein), 496
 Myopathy, flutter and auriculoventricular dissociation in patient with, 804⁺
 Myxedema with pericardial effusion, 803⁺
 Myxoma of heart (Brown), 373

N

- Neurectomy, pericoronary (Fauteux), 263
 combined with ligation of great cardiac vein, treatment of coronary disease with angina by (Fauteux), 260
 Neurocirculatory asthenia, unstable T waves in Leads II and III in persons with (Wendkos and Logue), 711
 Neurogenic, mechanical and, elements (II); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 282
 Nodal rhythm, chronic experimental, three observations on, by surgical ablation of sinus node, 804⁺
 Nodules in rheumatic fever, 110⁺
 Normal men, analysis of time relationships within cardiac cycle in electrocardiograms (Schlamowitz), 329, 464, 473
 Nutritional deficiency, relation of, to cardiac dysfunction, 525⁺

O

- Olive oil, effect of feeding, on absorption and deposition of cholesterol (VIII); experimental arteriosclerosis, 381
 Orthodiagraphic measurement of transverse diameter of heart, method for, by means of simple fluoroscope (Howard), 724
 Ossification of myocardium, primary, massive calcification with (Edelstein), 496
 Oxygen consumption, cerebral, cerebral blood flow, cardiac output, and blood pressure of normal young men, effects of hyperventilation of, 801⁺

P

- P wave, pulmonary, comparative study of, in chronic mitral and pulmonary disease, 108⁺
 Papaverine hydrochloride, death following intravenous administration of, 243⁺
 Paravertebral block and electrocardiogram in angina pectoris, 802⁺

- Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270, 282, 293
 tachycardia, abnormal electrocardiogram following recovery from (Ward), 645
 ventricular tachycardia (Freudlich), 557
 Patent ductus arteriosus complicated by presence of multiple congenital cardiac defects, cure of subacute bacterial endarteritis by surgical ligation in patient with (Ziegler), 231
 surgical therapy of, 110⁺
 Pathogenesis of pulmonary edema following bilateral vagotomy, studies on (Reichsman), 590
 Pathologic study of thirty-one cases of scrub typhus fever with especial reference to cardiovascular system (Levine), 314
 Penetrating wounds of chest, circulation in; study by method of right heart catheterization (Merrill et al.), 413
 Penicillin, clinical arrest of endocardial actinomycosis after forty-four million units of (Mac Neal et al.), 668
 ineffectiveness of, in some cases of bacterial endocarditis, 380⁺
 intrapericardial, pneumococcal pericarditis treated with, 381⁺
 Staphylococcus aureus septicemia and pericarditis treated with (Zimmerman and Durgin), 93
 treatment of subacute bacterial endocarditis, 384⁺ (Monroe), 651, 658⁺
 Perforation and death from cardiac tamponade, congenital defect of aortic vestibule complicated by bacterial endocarditis with (Medalia and Drapiewski), 103
 Pericardial effusion, myxedema with, 803⁺
 or empyema, pericardial tamponade from stab wound of heart and (Warren et al.), 418
 tamponade from stab wound of heart and pericardial effusion or empyema (Warren et al.), 418
 Pericarditis associated with uremia, electrocardiographic changes in (Keith et al.), 527
 constrictive, induced changes in circulation in, 803⁺
 metastatic carcinoma as cause of (Wallace and Logue), 223
 pneumococcal, treated with intrapericardial penicillin, 381⁺
 Staphylococcus aureus septicemia and, treated with penicillin (Zimmerman and Durgin), 93
 with effusion following infections of upper respiratory tract (Nathan and Dathe), 115

- Pericoronary neurectomy (Fauteux), 263
combined with ligation of great cardiac vein, treatment of coronary disease with angina by (Fauteux), 260
- Peripheral blood flow and rectal and skin temperatures in hypertension (Stewart et al.), 617
effect of splanchnic resection on (Stewart et al.), 728
under basal conditions in older male subjects with normal and elevated blood pressures (Stewart et al.), 343
vascular diseases, blood flow in (Goetz), 173
- Pharmacologic experiments (III); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 293
- Phlebomanometer, use of: normal venous pressure values and study of certain clinical aspects of venous hypertension in man (Winsor and Burch), 387
- Phlebothrombosis, early diagnosis of, 799
- Phosphorus poisoning, electrocardiographic changes resulting from (Dathe and Nathan), 98
- Physicians, coronary artery disease among, 243*
- Physiological responses, various, to mild exercise test, studies of (II); convalescence from surgical procedures, 249*
- Physiopathology and surgical treatment of congenital cardiovascular defects, 519*
- Plasma and blood volume determination in bilaterally vagotomized rats (Reichsman), 605
- Plethysmogram of toes during rest (Goetz), 148
- Pneumococcal pericarditis treated with intrapericardial penicillin, 381*
- Pneumococcus pneumonia, electrocardiographic changes during and after (Thomson et al.), 565
- Pneumonia, pneumococcus, electrocardiographic studies during and after (Thomson et al.), 565
- Pneumopericardium, 246*
- Pneumothorax, intrathoracic auscultation in, 800*
right and left, considerations of cardiac reaction to, 524-
- Poisoning, phosphorus, electrocardiographic changes resulting from (Dathe and Nathan), 98
- Polyarteritis nodosa, 520*
- Position of arm, effect of change of, upon blood pressure (Stein), 477
- Positive pressure respiration, certain effects of, on circulatory and respiratory systems (Carr and Essex), 53
- P-R interval, duration of, and its relationship to cycle length (R-R interval) (III); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 473
- Precordial leads in childhood; comment on presence of double upward deflections in leads from sternal region of normal children, 657*
multiple versus single, evaluation of use of, in conjunction with three limb leads, for practical clinical electrocardiography (Manchester and Ethridge), 633
- Pregnancy, cardiopulmonary function during, 251 (B. Rev.)
coarctation and acute dissection of aorta associated with, 247*
- Prothrombin time in normal subjects and in patients with arteriosclerosis, study of (Meyers and Poindexter), 27
variations in (Meyers and Poindexter), 29
- Pulmonary arterial pressure in dogs, measurement of, 107*
artery, contribution to study of congenital dilatation of, 656*
entire main, persistent right aortic arch with atresia of (Herbut and Fox), 490
edema following bilateral vagotomy, studies on pathogenesis of (Reichsman), 590
general considerations on mechanism of (Luisada and Sarnoff), 303
paroxysmal, consequent to stimulation of cardiovascular receptors; I. Effect of intra-arterial and intravenous infusions (Luisada and Sarnoff), 270
II. Mechanical and neurogenic elements (Luisada and Sarnoff), 282
III. Pharmacologic experiments (Luisada and Sarnoff), 293
embolism, is there vagal pulmonocoronary reflex in? (Malinow et al.), 702
ligation of inferior vena cava for prevention of, 243*
stenosis, pure congenital (Freed and Budnitz), 369
- Pulmonocoronary reflex, vagal, in pulmonary embolism? (Malinow et al.), 702
- Pulse rate and blood pressure in infancy and early childhood, 378*
reaction to performing step-up exercise on benches of different heights, 654*

Q

- Q-T interval, duration of, and its relationship to cycle length (R-R interval) (I); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 329

R

- Rate and control of blood flow through skin of lower extremities (Goetz), 146
- Raynaud's disease, part of venospasm in producing clinical picture of, 532*
- Receptors, cardiovascular, paroxysmal pulmonary edema consequent to stimulation of (Luisada and Sarnoff), 270, 282, 293
- Rectal and skin temperatures, effect of splanchnic resection on peripheral blood and, in hypertension (Stewart et al.), 728
- in hypertension, blood flow and (Stewart et al.), 617
- Resection, splanchnic effect of, on peripheral blood flow and rectal and skin temperatures in hypertension (Stewart et al.), 728
- Respiration, positive pressure, certain effects of, on circulatory and respiratory systems (Carr and Essex), 53
- Respiratory and circulatory systems, certain effects of positive pressure respiration on (Carr and Essex), 53
- tract, upper, pericarditis with effusion following (Nathan and Dathe), 115
- Rheumatic carditis, occurrence of, in native population of Curacao, Netherlands West Indies, 658*
- fever, acute, treatment of, with large doses of sodium salicylate, with special reference to dose management and toxic manifestations, 802*
- and rheumatic heart disease, Harveian oration on, 246*
- effect of salicylate therapy on Weltmann serum coagulation reaction and its use as prognostic test in, 656*
- etiology and pathogenesis of, 244*
- hypersensitivity and, 801*
- nodules in, 110*
- observations on treatment of, with vitamin P, 244*
- streptococcus infection and, some experimental aspects of, 110*
- studies in, 109*
- therapeutic value of early physical activity in, preliminary report, 384*
- heart disease associated with meningo-encephalitis, 113*

Rheumatic heart disease—Cont'd

- Harveian oration on rheumatic fever and, 246*
- in Denver school children, prevalence of, 250*
- recurrences in children, prevention of, by use of sulfathiazole and sulfadiazine, 379*
- Rheumatoid arthritis, characteristic vascular pattern in patients with, 380*
- Rhythm and conduction, multiple disturbances of, and unusual auricular T wave in case of myocardial infarction (Miller and Perelman), 501
- bigeminal, persistent ventricular, in apparently normal hearts, 659*
- R-R interval, cycle length, duration of P-R interval and its relationship to (Schlamowitz), 473
- duration of Q-T interval and its relationship to (Schlamowitz), 329
- duration of T-P interval and its relationship to (Schlamowitz), 464
- Rubella, maternal, congenital defects following, 256*

S

- Salicylate therapy, effect of, on Weltmann serum coagulation reaction and its use as prognostic test in rheumatic fever, 656
- Salt depletion and dehydration, hemodynamic changes in, 660*
- Scarlet fever, transitory A-V block occurring during (Paul et al.), 138
- Scrub typhus, congestive heart failure in (Levine), 325
- fever, electrocardiographic changes in (Hollander), 481
- pathologic study of thirty-one cases of, with especial reference to cardiovascular system (Levine), 314
- hemorrhagic phenomena in (Levine), 325
- pathologic changes in heart and other organs in (Levine), 315
- question of residual cardiac damage in (Levine), 326
- Sensations, subjective, associated with extrasystoles, study of (Kline and Bidder), 255
- Septicemia, *Staphylococcus aureus*, and pericarditis treated with penicillin (Zimmerman and Durgin), 93
- Serum thiocyanate, relationship of blood pressure and, 385*
- Shape, size and, of T wave, effect of exercise on (Dehn et al.), 188

- Shock, hemorrhagic, definition and criteria for its diagnosis, 660*
traumatic, in man, electrocardiograms in, 244*
- Shudder, carotid, 379*
- Sinoatrial, interatrial and, block, with illustrative case (Decherd et al.), 352
- Sinus arrhythmia and respiratory variation of ballistocardiogram, 659*
carotid, stimulation; hemiplegia following (Askey), 131
hyperactive carotid, reflex, angina pectoris, and myocardial infarction, case report of similar symptoms produced by (Glenn and Read), 792
- Size and shape of T wave, effect of exercise on (Dehn et al.), 188
- Skin and rectal temperatures, effect of splanchnic resection on peripheral blood flow and, in hypertension (Stewart et al.), 728
of lower extremities, rate and control of blood flow through (Goetz), 146
sensitivity, intolerance as shown by; mercurial diuretics, 378*
temperatures in hypertension, peripheral blood flow and (Stewart et al.), 617
- Smith, Fred M., 253
- Sodium restriction in diet for hypertension, 112*
salicylate, fatal thrombocytopenic purpura due to, 242*
treatment of acute rheumatic fever with large doses of, with special reference to dose management and toxic manifestations, 802
- South Pacific malaria, experience with (Sprague), 428
- Sphygmomanometer, differences in blood pressure values determined by inflating and deflating cuff of (Cunningham), 220
- Spinal anesthesia, high, effect of, on blood pressure of patients with hypertension and far-advanced renal disease—its possible relationship to pathogenesis of hypertension (V); studies in hypertension, 379*
- Splanchnic resection, effect of, on peripheral blood flow and rectal and skin temperatures in hypertension (Stewart et al.), 728
- Stab wound of heart and pericardial effusion or empyema, pericardial tamponade from; study utilizing method of right heart catheterization (Warren et al.), 418
- Staphylococcus aureus septicaemia and pericarditis treated with penicillin (Zimmerman and Durgin), 93
- Stenosis, congenital tricuspid, 525*
mitral, and arterial hypertension, 805*
pure congenital pulmonary (Freed and Budnitz), 369
- Stimulation, carotid sinus, hemiplegia following (Askey), 131
of cardiovascular receptors, paroxysmal pulmonary edema consequent to (Luisada and Sarnoff), 270, 282, 293
- Streptococcus, hemolytic, sore throat, abnormalities in electrocardiogram following, 658*
infection and rheumatic fever, some experimental aspects of, 110*
s.b.e. in subacute bacterial endocarditis, 383*
- Subendocardial and endocardial degeneration, mural thrombi, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Subjective sensations associated with extrasystoles, study of (Kline and Bidder), 254
- Sulfadiazine, prevention of rheumatic recurrences in children by use of, 379*
- Sulfathiazole, prevention of rheumatic recurrences in children by use of, 379*
- Surgical ablation of sinus node, three observations on chronic experimental nodal rhythm by, 804*
correction, experimental studies regarding; coarctation of aorta, 112*
for coarctation of aorta, 380*
ligation in patient with patent ductus arteriosus complicated by presence of multiple congenital cardiac defects, cure of subacute bacterial endarteritis by (Ziegler), 231
management of peripheral vascular disorders, 805**
procedures, convalescence from; I. Studies of circulation lying and standing, of tremor, and of program of bed exercises and early rising, 249*
II. Studies of various physiological responses to mild exercise test, 249*
- relief for tracheal obstruction from vascular ring, 113*
therapy of patent ductus arteriosus, 110*
treatment, congenital coarctation of aorta and, 381*
consideration of two cardiac diseases amenable to, 243*
of arterial hypertension, 521*
of essential hypertensive cardiovascular disease in man, experiences with, 245*
physiopathology and, of congenital cardiovascular defects, 519*
- Sympathectomized extremities, blood flow in (Goetz), 168

- Sympathotomy, bilateral cervical vagotomy and, in rat under ether anesthesia (Reichsman), 595
- Syndrome, anginal, treatment of, with thiouracil, 247*
- superior vena cava; report of thirty-five cases (Hussey et al.), 1
- Wolff-Parkinson-White, and related problems, 108*
- System, cardiovascular, pathologic study of thirty-one cases of scrub typhus fever with especial reference to (Levine), 314
- Systems, circulatory and respiratory, certain effects of positive pressure respiration on (Carr and Essex), 53
- T
- T waves, unstable, in Leads II and III in persons with neurocirculatory asthenia (Wendkos and Logue), 711
- unusual auricular, multiple disturbances of rhythm and conduction and, in case of myocardial infarction (Miller and Perelman), 501
- Tachycardia, paroxysmal, abnormal electrocardiogram following recovery from (Ward), 645
- ventricular (Freundlich), 557
- transient bundle branch block associated with (Eichert), 511
- ventricular—report on ten cases, eight of which were treated with quinidine with recovery in seven, 111*
- Tamponade, cardiac, congenital defect of aortic vestibule complicated by bacterial endocarditis with perforation and death from (Medalia and Drapiewski), 103
- pericardial, from stab wound of heart and pericardial effusion or empyema; study utilizing method of right heart catheterization (Warren et al.), 418
- Temperatures, rectal and skin, effect of splanchnic resection on peripheral blood flow and, in hypertension (Stewart et al.), 728
- in hypertension, peripheral blood flow and (Stewart et al.), 617
- Tetralogy of Fallot, ease of, 109*
- Thebesian veins, thromboses of, endocardial and subendocardial degeneration, and mural thrombi, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Therapeutic value of early physical activity in rheumatic fever, preliminary report, 384*
- Thiocyanate, serum, relationship of blood pressure and, 385*
- Thiouracil, treatment of anginal syndrome with, 247*
- Thoracic, right, and left cervical vagotomy (Reichsman), 600
- Thrombi, mural, endocardial and subendocardial degeneration, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Thrombocytopenic purpura, fatal, due to sodium salicylate, 242*
- Thromboembolic disease, venous, 521*
- Thromboplastic properties of some mercurial diuretics (Macht), 460
- Thromboses of thebesian veins, endocardial and subendocardial degeneration, and mural thrombi, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Time, prothrombin, in normal subjects and in patients with arteriosclerosis, study of (Meyers and Poindexter), 27
- relationships within cardiac cycle in electrocardiograms of normal men, analysis of (Schlamowitz), 329, 464, 473
- Tobacco, angina pectoris and, 525
- Toes, rate of blood flow in (Goetz), 158
- T-P interval, duration of, and its relationship to cycle length (R-R interval) (II); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 464
- Tracheal obstruction from vascular ring, surgical relief for, 113*
- Tracheobronchial tree, heart, and inferior vena cava of normal dogs, certain effects of positive pressure respiration on (Carr and Essex), 61
- Transfusion, blood, intracardiac, 385*
- Transient bundle branch block associated with tachycardia (Eichert), 511
- Transverse diameter of heart, method for orthodiagraphic measurement of, by means of simple fluoroscope (Howard), 724
- Trauma of limbs, acute hemorrhage or, effects of positive pressure respiration on circulation and respiration when combined with (Carr and Essex), 64
- vascular (II); surgical management of peripheral vascular disorders, 805*
- Traumatic shock in man, electrocardiograms in, 244*
- Tremor, circulation lying and standing, and bed exercises and early rising, studies of (I); convalescence from surgical procedures, 249*
- Triuspid stenosis, congenital, 525*
- Tsutsugamushi disease, cardiovascular disturbances in, 248*

Typhus fever, scrub, electrocardiographic changes in (Hollander), 481
 pathologic study of thirty-one cases of, with especial reference to cardiovascular system (Levine), 314

U

Unipolar derivation, critical study of, 108⁺
 Uremia, electrocardiographic changes in pericarditis associated with (Keith et al.), 527
 Urethane anesthesia, bilateral cervical vagotomy under (Reichsman), 599

V

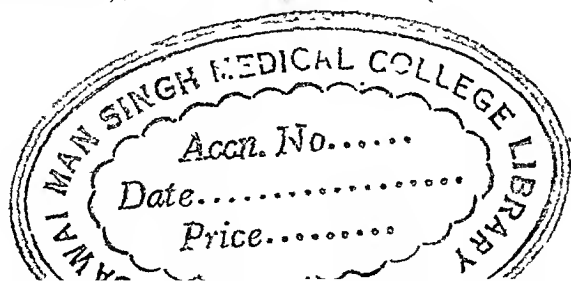
Vagal pulmonocoronary reflex in pulmonary embolism? (Malinow et al.), 702
 Vagotomized rats, bilaterally, plasma and blood volume determination in (Reichsman), 605
 Vagotomy, bilateral cervical, and sympathectomy in rat under ether anesthesia (Reichsman), 595
 under urethane anesthesia (Reichsman), 599
 studies on pathogenesis of pulmonary edema following (Reichsman), 590
 right thoracic and left cervical (Reichsman), 600
 Valve, mitral, calcification of (Fertman and Wolff), 580
 Vascular disorders, peripheral, surgical management of, 805⁺
 II. Vascular trauma, 805⁺
 pattern, characteristic, in patients with rheumatoid arthritis, 380⁺
 ring, surgical relief for tracheal obstruction from, 113⁺
 Vectorcardiogram, method for construction of, from Einthoven electrocardiogram (Howard), 191
 Vein, great cardiac, treatment of coronary disease with angina by pericoronary neurectomy combined with ligation of (Fauteux), 260
 coronary, ligation of, in man (Fauteux), 261
 Veins, thebesian, thromboses of, endocardial and subendocardial degeneration, and mural thrombi, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
 Vena cava, inferior, tracheobronchial tree, and heart, of normal dogs, effects of positive pressure respiration on (Carr and Essex), 61

Vena caval syndrome, superior; report of thirty-five cases (Hussey et al.), 1
 Venospasm, its part in producing clinical picture of Raynaud's disease, 521⁺

Venous filling, time of, 107⁺
 hypertension in man, normal venous pressure values and study of certain clinical aspects; use of phlebomanometer (Winsor and Burch), 387
 pressure, establishment of normal values for (Winsor and Burch), 395
 factors affecting (Winsor and Burch), 391
 in patients with right ventricular congestive heart failure (Winsor and Burch), 397
 pressures in disorders of venous system of lower extremities, 380⁺
 return, action of cardiac ejection on, 655⁺
 in absence of cardiac drive, 382⁺
 intra-abdominal pressure and regulation of, 107⁺
 thromboembolic disease, 521⁺
 Ventricle, cardiac, action of heat and cold on different components of electrogram of, 107⁺
 left, electrocardiographic effects of injury at endocardial surface of (Bayley), 677
 turtle, action of acetylcholine and epinephrine on, 381⁺
 Ventricular fibrillation (Parsonnet et al.), 769
 tachycardia, paroxysmal (Freudlich), 557
 treated with quinidine, 111⁺
 Veterans discharged because of heart disease or hypertension, re-examination of, 520⁺
 Vitamin P, observations on treatment of rheumatic fever with, 244⁺

W

Wolff-Parkinson-White syndrome and related problems, 108
 in association with congenital heart disease: coarctation of aorta (Bodlander), 785
 Wound, stab, of heart and pericardial effusion or empyema, pericardial tamponade from; study utilizing method of right heart catheterization (Warren et al.), 418
 Wounds, penetrating, of chest, circulation in; study by method of right heart catheterization (Merrill et al.), 413



centimeters of air were injected into the pericardial sac. Immediately after pericardiocentesis, metallic tinkles were heard, and the friction rub was prominent. The latter disappeared nine days later. The patient did well following this procedure, but there was a persistent tachycardia, varying from 100 to 130 per minute, while at rest in bed. The tachycardia gradually subsided, and the course of convalescence was essentially uneventful thereafter. The blood pressure was always between 100/70 and 120/80. The temperature was 102.2° F. on admission. There was a slight fluctuation between 99° and 102° F. for eight days and it was normal thereafter. The venous pressure was 10.5 cm. of blood on the fourth hospital day and rose to 20 cm. on the ninth hospital day. A total of 25 Gm. of sulfathiazole was given during the first week. Since there was no clinical improvement, the drug was discontinued.

Laboratory Findings.—The white blood cell count which was 16,400 per cubic millimeter on admission, rose to 27,400 on the seventh day, and gradually returned to normal. The differential count showed 85 to 95 per cent polymorphonuclear leucocytes. The red blood cell count was 4,250,000 per cubic millimeter with 85 per cent hemoglobin. The highest sedimentation rate was 27 mm. per hour. The sputum was negative for tubercle bacilli on three occasions. The blood serologic test was negative. The pericardial fluid contained a large number of red blood cells, occasional lymphocytes, and serosal cells. The stain and culture for acid-fast and nonspecific organisms were sterile. A guinea pig inoculation was negative for tuberculosis (Fig. 1).

X-Ray Examinations.—On March 14, 1943, the transverse cardiac diameter measured 15.7 centimeters. There was fullness and prominence of the left ventricle, and the right cardiophrenic angle was obtuse. The hilum shadows were accentuated, and there were heavy peribronchial vascular markings radiating into the lung field. The cardiothoracic ratio was 65 per cent. Following the pericardial tap, the heart size seemed to be within normal limits. The pericardium was well visualized and appeared to be considerably thickened. On May 30, 1943, the transverse diameter of the heart measured 12.2 cm. and was essentially normal in size and shape.

Electrocardiographic Findings.—On March 12, 1943, there was some straightening of the S-T segments in Leads I and II, but no significant elevation. The Q₃ measured 1½ mm., and T₃ was inverted. On March 29, 1943, the descending limb of T₁ was diphasic. The T₂ was inverted, and T₄ was isoelectric. On May 19, 1943, the T₁ was upright, T₂ was diphasic, and T₃ was inverted (Fig. 2).

CASE 2.—A 28-year-old white man was admitted to the hospital on March 13, 1943. About 3:00 A.M. on the day of admission, the patient was awakened with a severe pain in the chest and left upper abdomen. The pain was agonizing in character and made worse by deep inspiration or by attempting to lie flat in bed. Relief was obtained by sitting up and crouching forward. A sore throat was present five days prior to admission.

Physical Examination.—The patient was acutely ill, the skin was cold and clammy, and the blood pressure measured 110/70. There was a loud pericardial friction rub present over the entire precordium but most intense at the apex. The remainder of the physical examination was essentially negative.

Course.—The pericardial friction rub remained for about twelve hours after admission. The liver became palpable after twenty-four hours and was slightly tender. The temperature varied from normal to 102° F. for about two weeks, after which a low-grade fever to 99.6° F. persisted until the fifth week of illness. The liver remained palpable for several weeks. Convalescence was slow but finally complete.

X-Ray and Fluoroscopic Examinations.—On March 14, 1945, the heart was symmetrically enlarged in all directions with encroachment on the posterior clear space. Fluoroscopy revealed feeble cardiac pulsations on admission with progressive improvement in the amplitude of the ventricular systole as the patient improved.

Electrocardiographic Findings.—On March 13, 1944, there was an elevation of the S-T segments in Leads I and II of 1 and 2 mm., respectively. The S-T₄ was straight. On March 15, 1944, there was a slight increase in the elevation of the S-T₁ and the S-T₂. On March 22, 1944, the descending limbs of T₁ and T₂ showed a diphasic tendency. By March 29, 1944, T₁,

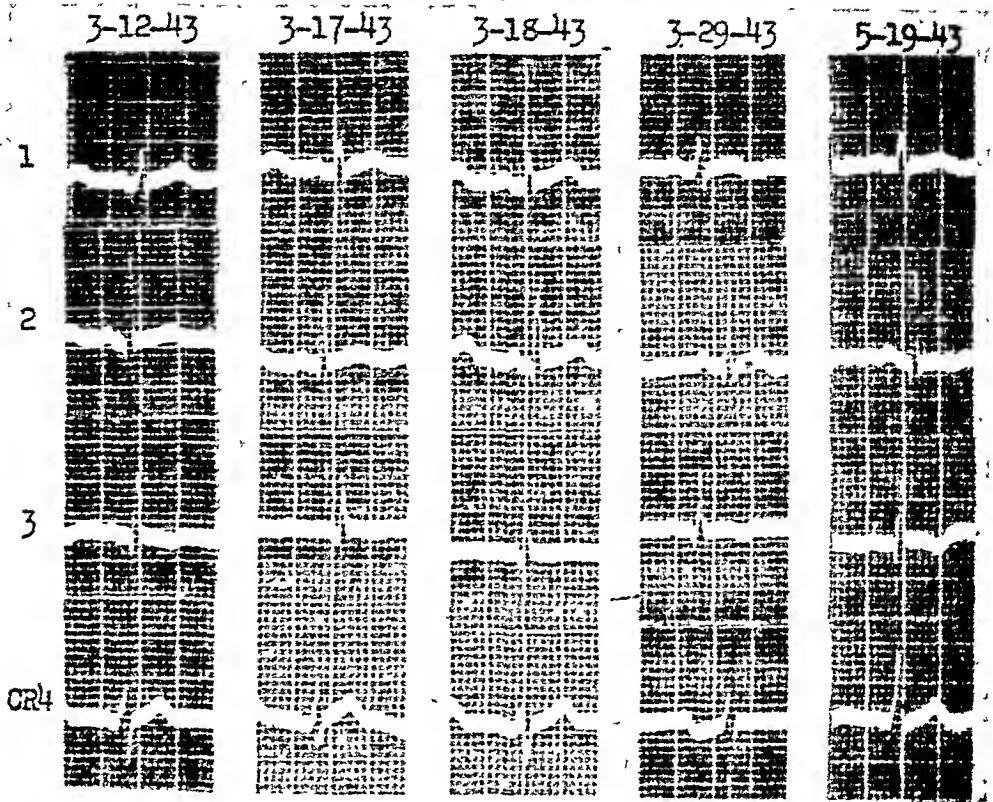


Fig. 2.—Case 1. There is progressive inversion of the T waves in all leads with somewhat straightened and elevated S-T segments particularly in Leads I and II. (Lead CR₄ taken on March 29, 1943, is upside down.)

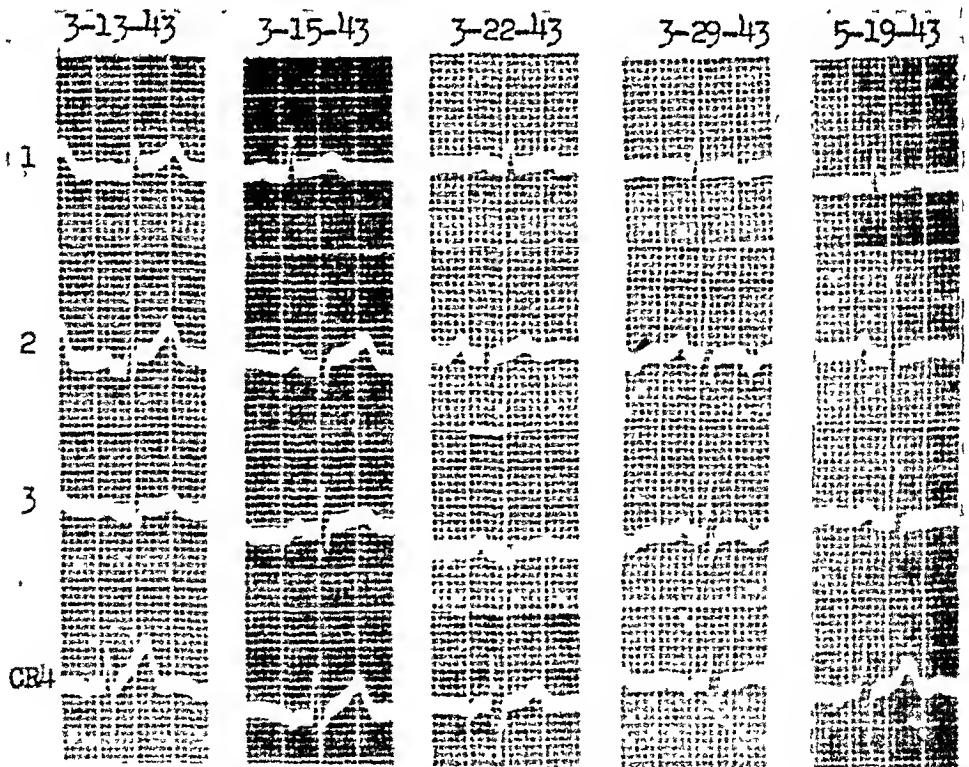


Fig. 3.—Case 2. There is high take-off of ST₁ segments in the electrocardiogram taken on March 13, 1944. This is followed by progressive inversion of the T waves and subsequent return to normal.

T₂, and T₃ were inverted. An electrocardiogram taken on May 19, 1944, was essentially normal except for the low voltage of T₂ and an isoelectric T₃ (Fig. 3).

CASE 3.—A 21-year-old white man was admitted to the hospital on July 20, 1943. He became ill on June 11, 1943, with acute nasopharyngitis, at which time he was admitted to the hospital and treated with a total of 28 Gm. of sulfathiazole. The recovery was uneventful. The chest was negative at the time of discharge from the hospital on July 2, 1943. On readmission, he complained of severe, substernal pain which was aggravated by the slightest motion and by deep inspiration. On the first hospital day, the patient was acutely ill with a temperature of 102° F. and a mild cyanosis of the lips and fingernails. The severe pain in the chest persisted and spread to the left side. Nineteen days after admission, fluid developed in the left thorax. Four hundred cubic centimeters of slightly cloudy amber fluid were removed. The precordial pain persisted, although no pericardial friction rub was heard. There was gradual decrease in the size of the heart, and the patient made an uneventful recovery. The temperature fluctuated from 100° to 102.2° F. several days before returning to normal.

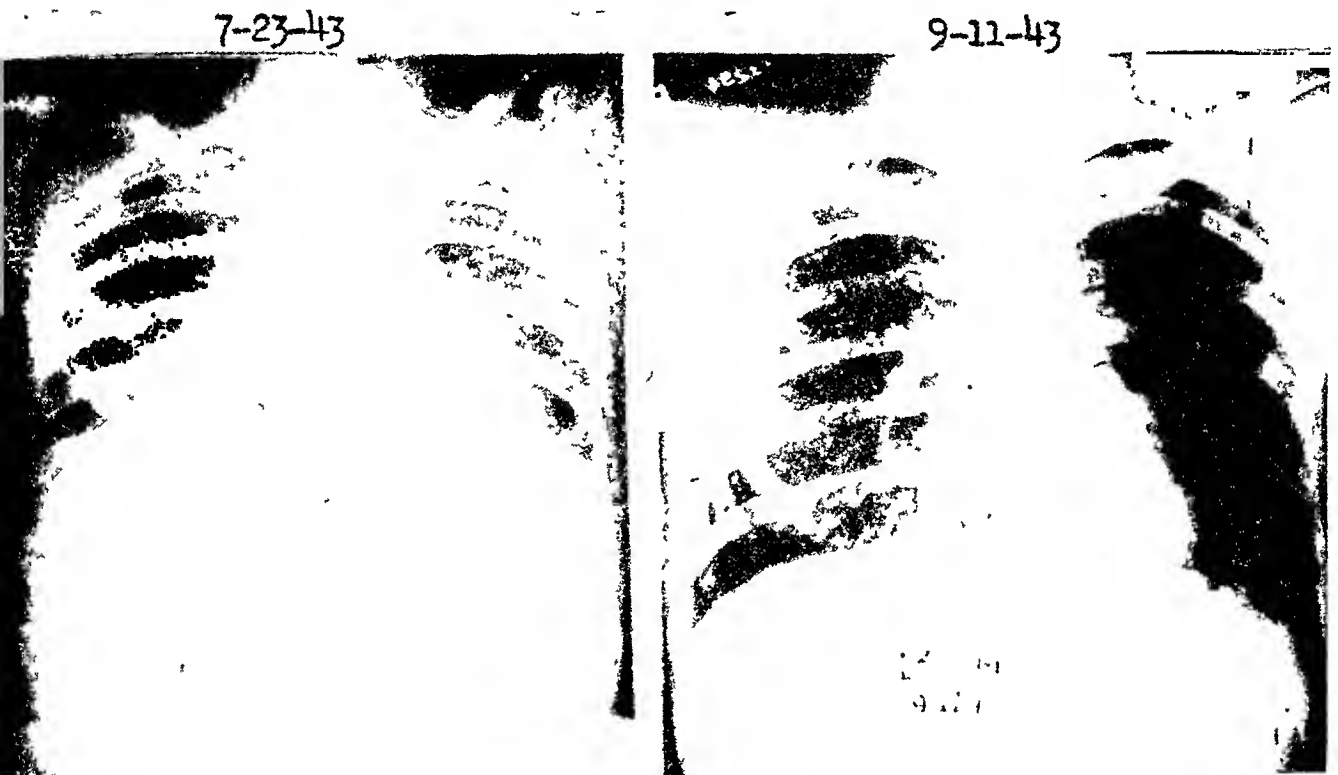


Fig. 4.—Case 3. Marked enlargement of the cardiac shadow and return to normal. The cardiophrenic angles are obscured by marked congestive changes in the film taken on July 23, 1943.

Laboratory Findings.—The white blood cell count was 12,000 per cubic millimeter with 79 per cent polymorphonuclear leucocytes and 17 per cent lymphocytes. The red blood cell count was 4,940,000 cubic millimeters with 94 per cent hemoglobin. The leucocyte count rose to 22,600 on the sixth hospital day and gradually returned to normal. The nonprotein nitrogen of the blood was 48.4 mg. per cent. The blood culture was sterile. The highest sedimentation rate was 8 mm. per hour. The pleural fluid had a specific gravity of 1.015 with 3,200 white blood cells per cubic millimeter. The differential count of the pleural fluid showed 85 per cent lymphocytes and 14 per cent polymorphonuclear leucocytes. The stained film, culture, and guinea pig inoculation showed no evidence of tuberculosis after eight weeks.

X-Ray and Fluoroscopic Examinations.—On July 23, 1945, the transverse cardiac diameter measured 16.1 centimeters. The left border of the heart was somewhat convex in the region of the left auricle and the pulmonary conus. The cardiophrenic angles were not clearly defined. Evidence of congestive changes in both hilar regions was present.

Fluoroscopy revealed a very slight pulsation of the left ventricular systole. On Sept. 11, 1943, the transverse cardiac diameter measured 12.3 centimeters. The heart and lung fields were within normal limits (Fig. 4).

Electrocardiographic Findings.—On July 21, 1943, there was straightening of the S-T segments in Leads I and II with slight elevation of S-T₁ and S-T₂. There was a gradual reversal of the axis of T₁ and T₂ to negativity by Aug. 10, 1943. On Oct. 20, 1943, T₁ was still low in voltage (Fig. 5).

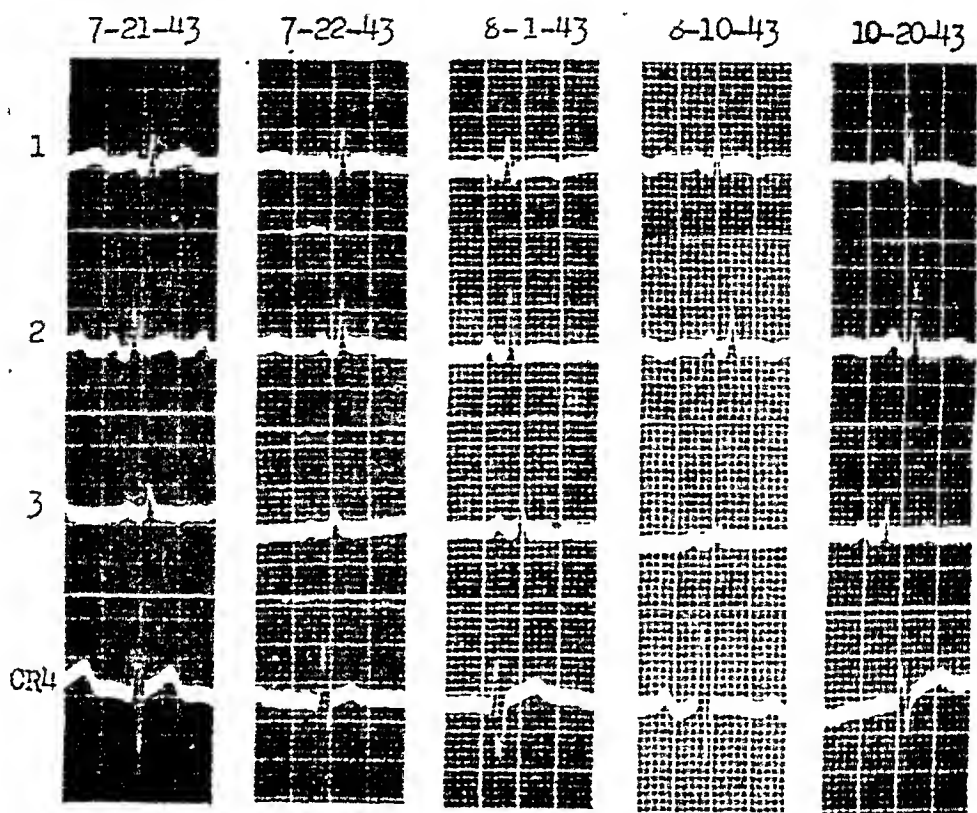


Fig. 5.—Case 3. Early changes consist of straightening and elevation of ST₁ and ST₂; later there is inversion of the T waves in Leads I and II.

CASE 4.—A 36-year-old white man was admitted to the hospital on Sept. 13, 1943. The onset of the illness occurred about two weeks prior to admission when substernal pain developed. The pain started after arising from bed and became progressively worse during the day. He was forced to take shallow breaths and flex his body forward to relieve the pain. The patient stated that he felt as if his chest was being torn away. There was some referred pain to the neck, shoulders, and arms. The previous personal history was essentially negative except for typhoid fever in 1925.

Physical Examination.—The blood pressure was 128/75. There was a moderately low-pitched to-and-fro scratchy roughened sound just to the left of the xiphoid. No murmurs were present. The remainder of the physical examination was essentially negative.

Course.—The pericardial friction rub was present for twelve days after admission. Three days after admission a pericardial aspiration was done, and 50 c.c. of hemorrhagic fluid were removed. The clinical course was uneventful thereafter, and the patient was discharged from the hospital on Nov. 8, 1943.

Laboratory Findings.—The highest white blood cell count was 11,000 per cubic millimeter. The erythrocytes numbered 4,900,000 per cubic millimeter with 85 per cent hemoglobin. The differential counts were within normal limits. The highest sedimentation rate was 24 mm. per hour. The pericardial fluid was hemorrhagic with a hematocrit of 10. Micro-

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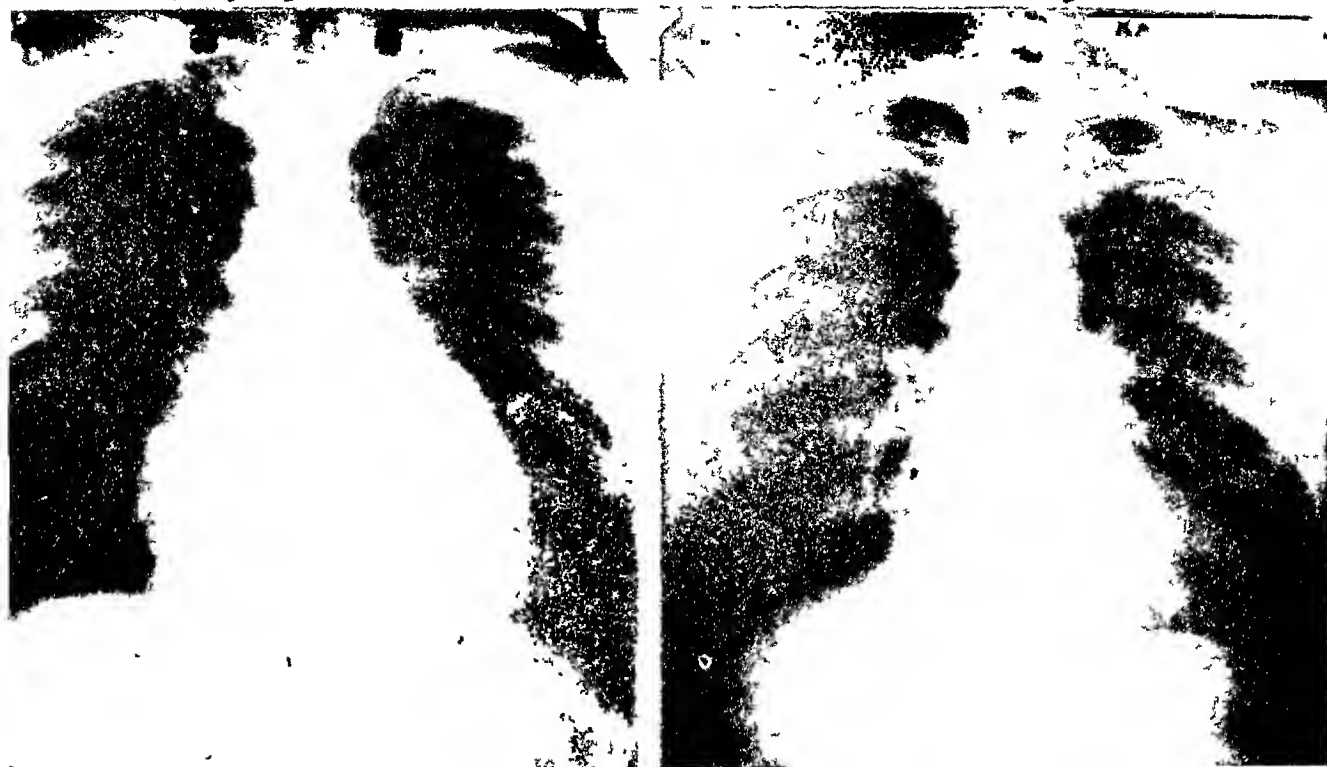


Fig. 6.—Case 4. Note "water bottle" configuration of the heart in the film taken on Sept. 13, 1943, and subsequent return to normal.

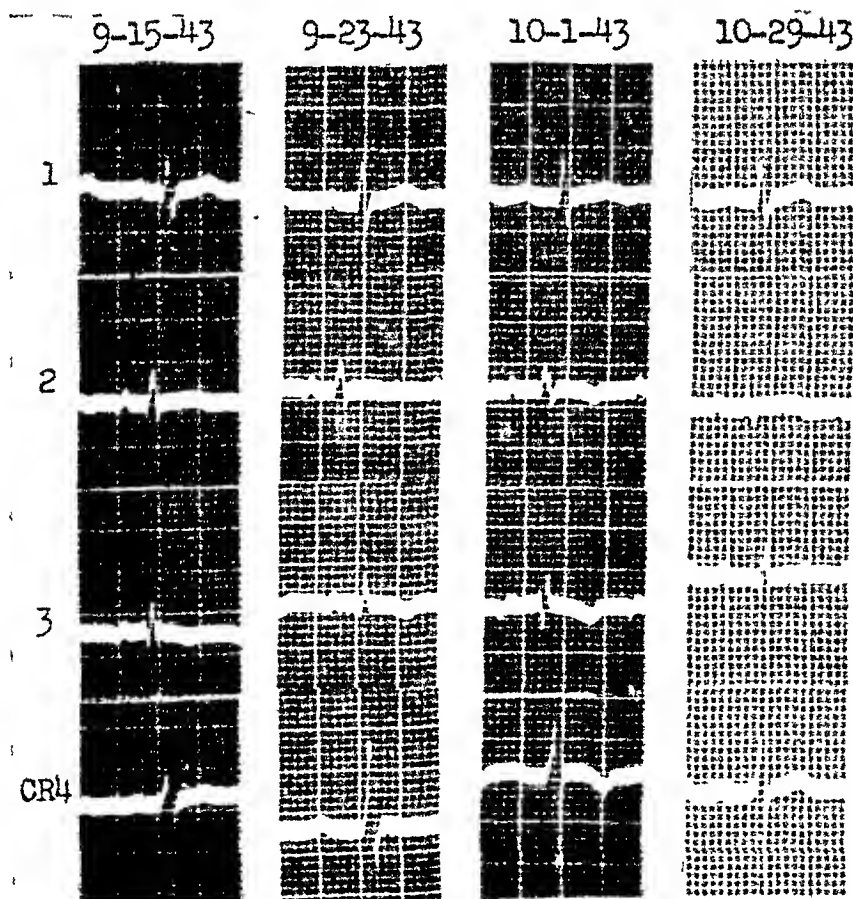


Fig. 7.—Case 4. The most marked changes consist of progressive inversion of the T waves in Leads II, III, and IV.

scopic examination showed laked red blood cells, a few polymorphonuclear leucocytes, and an occasional monocyte. The film and culture were sterile. The inoculated guinea pig was negative for tuberculosis.

X-Ray and Fluoroscopic Examinations.—On Sept. 13, 1943, the transverse cardiac diameter was 19.5 centimeters. There was a "water bottle" configuration of the cardiac shadow with fullness of both lower heart borders and straightening of the left cardiac waistline. The cardiothoracic ratio was 19.5:31.5 centimeters. The lung fields were essentially clear except for some generalized accentuation of the bronchovascular markings (Fig. 6). Fluoroscopy revealed feeble cardiac pulsations along the left cardiac border and some fullness posteriorly in the left oblique position. Considerable broadening of the supercardiac shadow was noted in the Trendelenburg position. On Oct. 18, 1943, the heart and lung fields were essentially normal. The transverse cardiac diameter measured 13.4 cm. (Fig. 7).

Electrocardiographic Findings.—On Sept. 15, 1943, the T_2 and T_4 waves showed low voltage, and T_3 was slightly inverted. Thereafter T_2 , T_3 , and T_4 showed progressive inversion. On Oct. 29, 1943, the descending limb of T_2 was diphase, and the voltage of T_3 was low.

CASE 5.—A 32-year-old white man was admitted to the hospital on Jan. 18, 1944. One week prior to admission he developed a "cold" and sore throat followed by substernal pain which was severe at times and accentuated by cough, by deep inspiration, or by motion of the body. The pain lasted three or four days. The past history was essentially negative.

Physical Examination.—The apex of the heart was percussed 11 cm. from the midsternal line in the fifth intercostal space. The sounds were slightly distant, but no murmurs were present. The rhythm was regular, the heart rate was 100 per minute, and the blood pressure was 120/75.

Course.—Nine days after admission a pericardiocentesis was performed and 175 c.c. of hemorrhagic fluid were removed. Seventy-five cubic centimeters of air were injected into the pericardial sac. Much fluid remained, however, after this aspiration. On the twelfth hospital day a friction rub was heard over the xiphoid and at the base of the heart in the midsternal line. It was present for six days. Fluoroscopy of the heart showed almost complete refilling of the pericardial sac with complete resorption of air. There was progressive diminution of the heart shadow thereafter, and the pulsations gradually increased in force and amplitude. The patient was discharged to furlough on May 6, 1944. Upon returning, there was a recrudescence of symptoms. Fluoroscopy of the heart showed a recurrent pericardial effusion. Spontaneous subsidence of this phase of illness occurred twenty-seven days later.

Laboratory Findings.—The highest white blood cell count was 8,500 per cubic millimeter with an essentially normal differential count. The erythrocytes numbered 4,150,000 per cubic millimeter with 85 per cent hemoglobin. The highest sedimentation rate was 21 mm. per hour. The pericardial fluid was hemorrhagic with a hematocrit of 6. The fluid contained mostly lymphocytes, many red blood cells, and an occasional polymorphonuclear leucocyte. The slide film and culture of the fluid were negative. A guinea pig inoculation with the fluid was negative for tuberculosis.

X-Ray Findings.—On Jan. 25, 1944, the transverse cardiac diameter measured 18.3 centimeters. The heart was globular in shape. The hilum markings were accentuated. On Jan. 28, 1944, after pericardiocentesis, there was a moderate amount of air in the pericardial sac along the left heart border. Moderate accentuation of the hilum markings persisted. On June 28, 1944, the transverse cardiac diameter measured 14.4 centimeters. The heart was essentially normal, although accentuation of the right hilum shadow was still evident (Fig. 8).

Electrocardiographic Findings.—On Jan. 22, 1944, there was slight elevation of the S-T segments in Leads I and II. On Feb. 3, 1944, T_1 was inverted. The S-T₂ was straight with an elevation of 1 millimeter. On Feb. 26, 1944, T_1 was low in voltage but upright. T_2 and T_3 were inverted. On April 10, 1944, the electrocardiogram was essentially normal (Fig. 9).

CASE 6.—A 31-year-old white man was admitted to the hospital on Jan. 20, 1944. He was well until forty-five days before admission, when he developed malaise, fever, slight cough, and vague fleeting chest pains. In the latter part of November, 1943, he developed a "cold" which did not subside. On Dec. 25, 1943, he was seized with severe substernal pain which did



Fig. 8.—Case 5. The cardiodiaphragmatic angles remain acute although marked pericardial effusion is present. This x-ray was made on Jan. 28, 1944, after aspiration of 175 c.c. of hemorrhagic fluid and injection of 75 c.c. of air into the pericardial sac.

not radiate. It was aggravated by inspiration or motion. The pain was frequently relieved by sitting forward. There was a loss of 15 pounds of weight prior to hospitalization. The past history was essentially negative.

Physical Examination.—The heart sounds were somewhat muffled, but otherwise not remarkable. There was no pericardial friction rub. The liver was palpable 4 cm. below the costal margin in the anterior axillary line. The remainder of the physical examination was essentially negative. The blood pressure was 115/90.

Course.—The patient was observed until Feb. 24, 1944, when he was transferred to a general hospital. There was gradual improvement, although the liver remained palpable and slightly tender. After the fourteenth hospital day, the muffled heart sounds disappeared. Thereafter, the sounds were essentially normal.

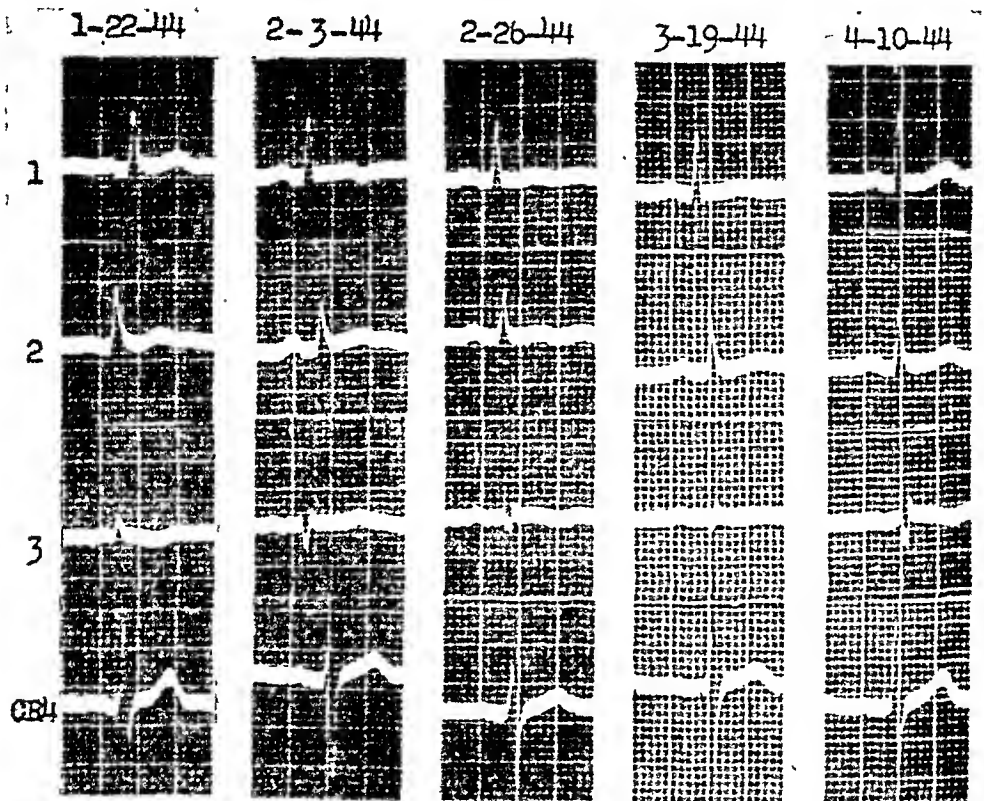


Fig. 9.—Case 5. There is progressive inversion of T_1 and T_2 in the first two tracings with subsequent return to normal.

Laboratory Findings.—The leucocyte count was 12,400 per cubic millimeter on admission with an essentially normal differential count. The erythrocytes numbered 4,500,000 per cubic millimeter with 95 per cent hemoglobin. The sedimentation rate was 15 mm. per hour on admission and remained at that level throughout his illness.

X-Ray and Fluoroscopic Examinations.—On Jan. 29, 1944, there was symmetrical enlargement of the heart with fullness of the left cardiac border. The transverse diameter of the heart measured 16.5 centimeters. The cardiothoracic ratio was 0.65. On Feb. 15, 1944, there was regression of the heart size to normal limits. Routine fluoroscopic examination revealed an absence of cardiac pulsations during the first fourteen days of hospitalization with subsequent return to normal pulsations thereafter.

Electrocardiographic Findings.—On Jan. 5, 1944, fifteen days prior to admission, an electrocardiogram was essentially negative. Seven days after admission, Jan. 27, 1944, T_1 was slightly inverted while T_2 and T_3 were inverted. There were notching and low voltage of T_4 . On Jan. 31, 1944, the T waves were inverted in the limb leads while T_4 showed notching.

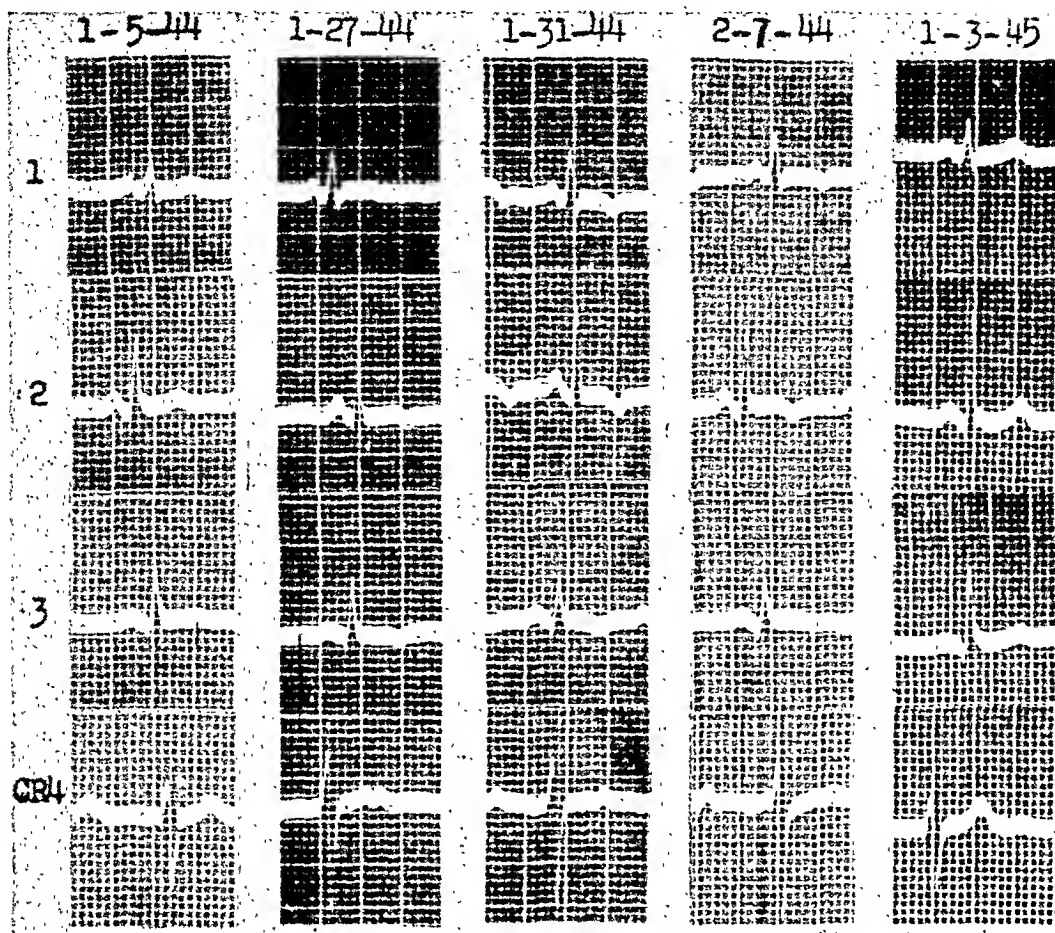


Fig. 10.—Case 6. There is progressive inversion of the T waves in all leads. Electrocardiogram of Jan. 3, 1945, was taken after complete clinical recovery.



Fig. 11.—Case 7. There is moderate enlargement of the cardiac shadow with subsequent return to normal.

There was little improvement on Feb. 7, 1944, but on Jan. 3, 1945, the electrocardiogram was normal (Fig. 10).

CASE 7.—A 22-year-old white man was admitted to the hospital on April 26, 1944, with fever and chills of three days' duration associated with severe, substernal pain aggravated by deep inspiration. He had had a sore throat fourteen days before admission. The past history was essentially negative.

Physical Examination.—The patient was acutely ill with slight cyanosis of the face and lips. The heart was essentially normal except for a tachycardia of 120 per minute. The blood pressure was 125/70.

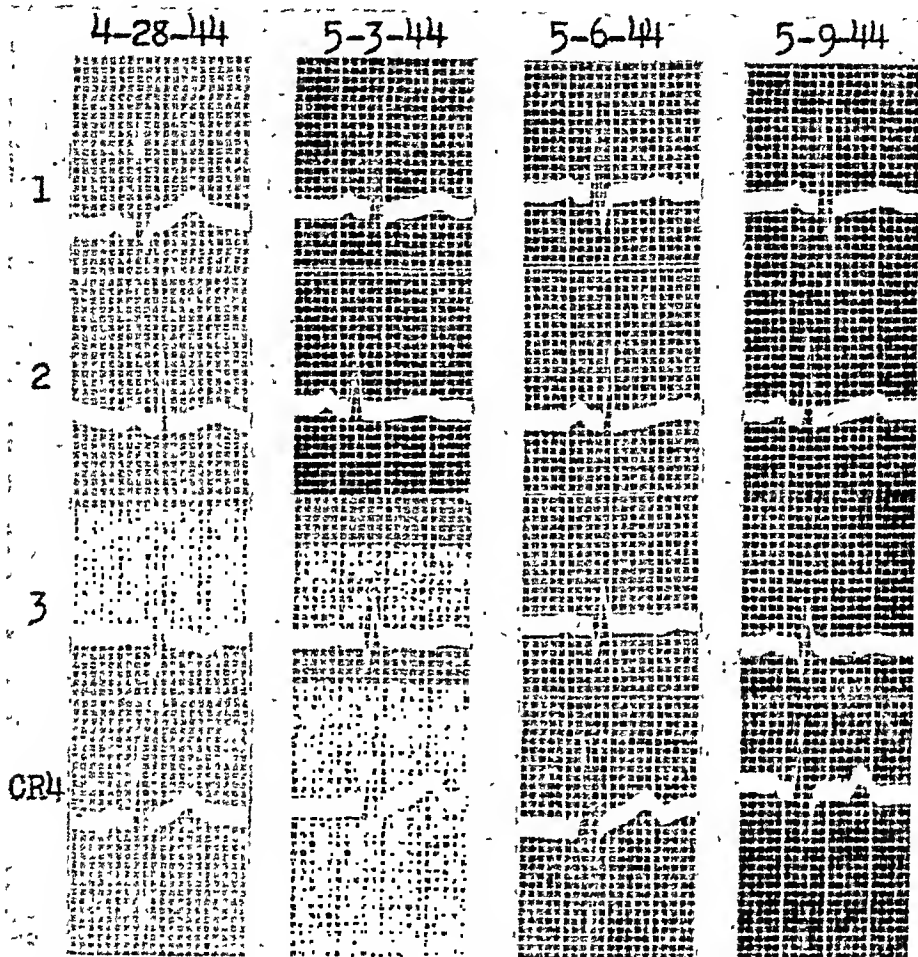


Fig. 12.—Case 7. There is a progressive decrease in the voltage of T_1 and T_2 . Note straightened S-T segments in Leads I and II of electrocardiograms taken on May 6, 1944, and May 9, 1944.

Course.—Soon after admission the precordial pain disappeared. A pericardiocentesis was performed two days after admission, and 10 c.c. of clear amber fluid were removed. On the eleventh hospital day, the patient complained of pain in the left chest, and a small amount of fluid was found at the left costophrenic angle. This cleared within a few days, and the subsequent course was uneventful. The temperature varied from 100° to 102° F. for five days and was normal thereafter.

Laboratory Findings.—The highest leucocyte count was 20,600 per cubic millimeter with 92 per cent neutrophils and 80 per cent lymphocytes. The highest sedimentation rate was 25 mm. per hour. The urinalysis was negative. The pericardial fluid showed a cell count of 1,000 per cubic millimeter with 96 per cent polymorphonuclear leucocytes and 4 per cent

lymphocytes. The slide film and culture of the fluid were essentially negative. Guinea pig inoculation with fluid was negative for tuberculosis (Fig. 11).

X-Ray and Fluoroscopic Examinations.—On April 27, 1944, the heart was enlarged to the left with no characteristic changes in contour. The transverse cardiac diameter measured 17.3 centimeters. The cardiothoracic ratio was 0.56. The lung fields were clear. On fluoroscopy, markedly diminished pulsations were present, and a posterior bulge of the pericardium was noted in the left oblique and lateral views. On May 15, 1944, the heart was normal in size and shape. The transverse cardiac diameter measured 14.7 centimeters.

Electrocardiographic Findings.—On April 28, 1944, Q_2 measured 3.5 millimeters. T_1 was inverted; S-T₁ was slightly straighter than usual. On May 3, 1944, there was a decrease in the voltage of T_1 and T_2 . T_3 was less inverted, and then measured 2 millimeters. On May 6, 1944, there was a low voltage of T_1 and T_2 with straightening of the S-T segments in Lead II. On May 9, 1944, there was no change in the electrocardiogram (Fig. 12).

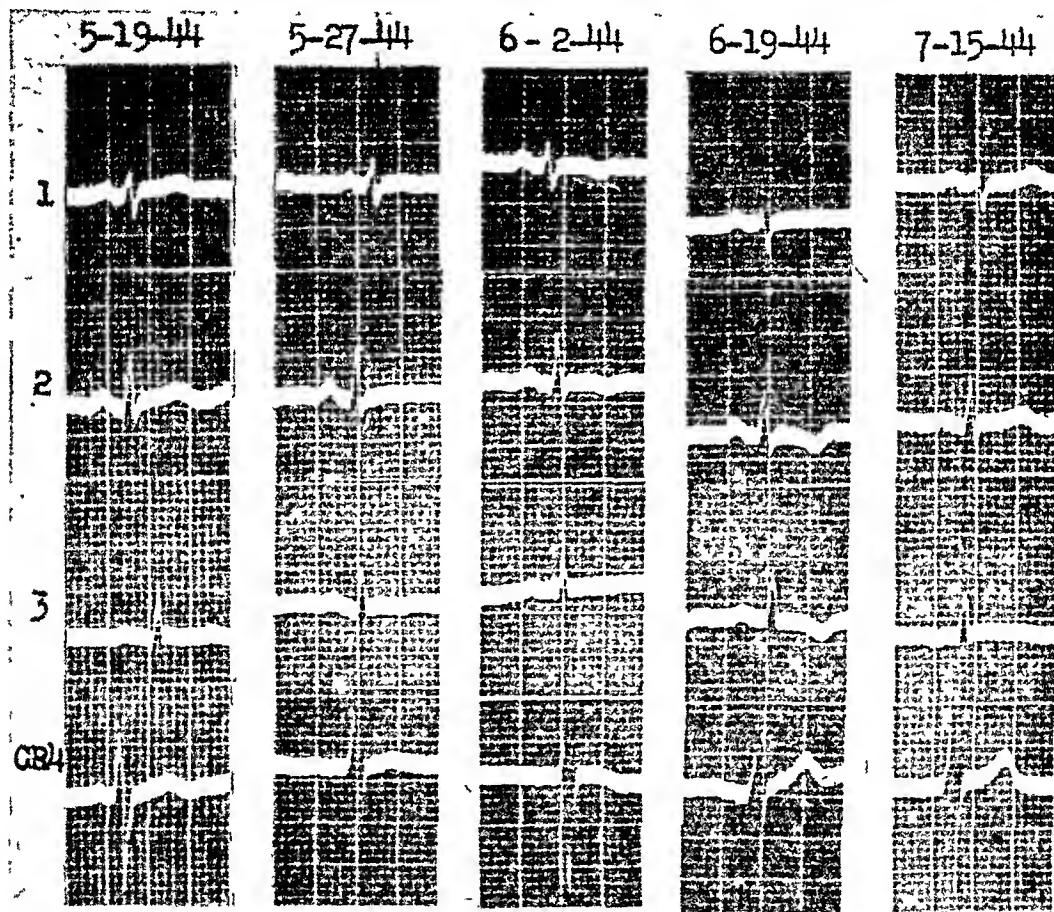


Fig. 13.—Case 8. There is progressive inversion of the T waves in all leads. Electrocardiogram of July 15, 1944, was taken after complete clinical recovery.

CASE 8.—A 33-year-old white man was admitted to the hospital on May 14, 1944. He became ill about four days prior to admission with substernal pain accentuated by deep inspiration and change of position particularly when recumbent. There was no definite history of an upper respiratory infection, although cough was present at the onset. The pain subsided slightly before admission to the hospital.

Past History.—He had had measles, mumps, and chicken pox in childhood. An appendectomy was performed in 1933. There were gonorrheal infections in 1936 and 1937. There was no history of rheumatic fever or tuberculosis.

Physical Examination.—There was a to-and-fro pericardial friction rub heard over the sternum at the level of the fourth rib in the midsternal line. The remainder of the physical examination was essentially negative.

Course.—A pericardiocentesis was done on May 25, 1944, and 3 c.c. of hemorrhagic fluid was obtained. This was repeated the next day, and 40 c.c. of similar fluid was recovered. A pericardial friction rub was present the first seventeen days of illness. Thereafter, the substernal pain disappeared, and the cardiac shadow receded to normal size. On the thirty-fourth hospital day, there was a recrudescence of fever and substernal pain. A friction rub was again heard over the left sternal border. The liver was felt 1 fingerbreadth below the costal margin in the anterior axillary line. Five days later the pericardial friction rub disappeared; the symptoms subsided, and recovery was uneventful.

Laboratory Findings.—The highest leucocyte count was 6,000 per cubic millimeter with 64 per cent neutrophils, 22 per cent lymphocytes, 10 per cent monocytes, and 4 per cent eosinophiles. The white blood cell count varied between 6,000 and 3,800 per cubic millimeter. The erythrocytes numbered 4,400,000 per cubic millimeter with 85 per cent hemoglobin. The serologic test for syphilis was negative. The highest sedimentation rate was 20 mm. per hour. The pericardial fluid contained 695,000 red blood cells per cubic millimeter with a hematocrit of 6. There was evidence of old hemolysis. The slide film and culture of the fluid were negative. Guinea pig inoculation with the fluid was negative for tuberculosis.

X-Ray and Fluoroscopic Examinations.—On May 19, 1944, the heart was quite large with fullness of both lower cardiac borders and in the region of the pulmonary conus. On May 25, 1944, fluoroscopy showed diffuse enlargement of the heart shadow to the right and left with marked diminution in the amplitude of the ventricular systole. In the lateral view there was prominent bulging posteriorly. In the Trendelenburg position, the retrosternal width increased about 2 centimeters. On May 27, 1944, after pericardiocentesis, there was a small amount of air visible along the left border of the heart. On May 31, 1944, fluoroscopy showed a uniform enlargement of the cardiac shadow in all views with marked diminution in all pulsations. On June 13, 1944, there was a slight prominence of the pulmonary conus but no evidence of pericardial effusion. The heart was essentially normal. Subsequent x-ray films taken on July 12, July 19, and July 24, 1944, showed the heart to be normal in size.

Electrocardiographic Findings.—On May 19, 1944, there was slight elevation and straightening of the S-T segments in Leads I and II. T_1 was isoelectric. On May 27, 1944, T_1 was isoelectric. T_2 showed low voltage; T_3 was diphasic. On June 2, 1944, the T waves were inverted in Leads I and II; T_4 was slightly inverted. On June 19, 1944, T_1 was upright but low in voltage. T_2 and T_3 were markedly inverted with slight depression of S-T₂ and S-T₃. T_4 was upright. On July 15, 1944, the electrocardiogram was essentially normal (Fig. 13).

REVIEW OF CASES

Seven of the eight patients were admitted to the hospital during the months of high respiratory incidence (Table I). In case 3 the patient was admitted during July, 1943, but there was a history of acute nasopharyngitis nine days before admission. In six cases there was an unequivocal history of tonsillitis, pharyngitis, or nasopharyngitis. Two patients (Cases 4 and 8) had a nonproductive cough but no history of an antecedent upper respiratory infection.

Evidence of our diagnoses was manifested by a pericardial friction rub in five cases associated with severe substernal pain which was the initial complaint in each. The highest leucocyte counts varied from 6,000 to 27,400 per cubic millimeter. In five of eight cases, x-ray films were available for mensuration, while films in Cases 2 and 8 were not obtainable from the Veterans' Administration files. The measurement of the transverse cardiac diameter was possible in one original x-ray film in Case 1. Significant recession of cardiopericardial shadow is demonstrated in the illustrations in Cases 1, 3, 4, 5, and 7. Pericardiocentesis was performed in five cases. The fluid was hemorrhagic in four patients and clear amber in one. The red blood cells were hemolyzed, and

TABLE I. SUMMARY OF CASES OF PERICARDITIS WITH EFFUSION

CASE	DATE OF ADMIS- SION	RESPIRA- TORY INFECTION	PRE- CORDIAL FRIC- TION RUB	SUB- STERNAL PAIN	LEUCO- CYTES (PER CU. MM.)	HEART DI- AMETER (CM.)	PERICARDIAL FLUID	
							SEDIMENT	FILM CULTURE GUINEA PIG
1	3/11/43	Yes	Yes	++++	27,400	15.7	Reddish amber; laked R.B.C.; occasional lymph- ocytes and serosal cells	0
2	3/13/43	Yes	Yes	++++			No	
3	7/20/43	Yes	No	++++	22,600	16.1 12.3	No	
4	9/13/43	No (Cough)	Yes	++++	11,000	19.5 13.4	Hemorrhagic fluid; laked R.B.C.; hematocrit 10; few polys; occasional monocytes	0
5	1/18/44	Yes	Yes	++++	8,500	18.3 14.4	Hemorrhagic fluid; laked R.B.C., lymphs, and occa- sional polys; hematocrit 6	0
6	1/20/44	Yes	No	++++	12,400	16.5	No	
7	4/26/44	Yes	No	++++	20,600	17.3 14.7	Clear yellow fluid; cell count 1,000 per cubic millimeter with 96 per cent polys; 4 per cent lymphs	0
8	5/14/44	No (Cough)	Yes	++++	6,000		Hemorrhagic fluid; laked R.B.C.; R.B.C. count 695,000; hematocrit 6	0

the hematocrit varied from 6 to 10. Slide film, culture, and guinea pig inoculation of the pericardial fluid were negative for bacteria in all cases.

The commonest change in the electrocardiograms was a progressive inversion of the T waves, straightening of the S-T segments in seven cases, and the elevation of the S-T segments (0.5 to 2 mm.) in five cases.

COMMENT

Reports concerning the association of acute pericarditis with effusion to upper respiratory infections are not numerous. Willius² reported a single case of acute serofibrinous pericarditis following acute pharyngitis which he believed is a common form of pericarditis. The nature of the infecting organism was thought to be a streptococcus invading the pericardium. Levine³ referred to a type of pericardial effusion due to a streptococcus infection but the effusion, however, was purulent. He considered the clinical condition a part of a generalized streptococcal infection which was associated especially with an antecedent sore throat. He also considered a virus infection as a possible etiological factor which does not produce empyema, shows no stigma of rheumatism, but resembles acute coronary occlusion. Wolff⁴ reported five cases of pericarditis during an acute upper respiratory infection. Three cases were associated with atypical pneumonia.

In considering the pathogenesis of this condition in this series, two possibilities are considered: (1) The proximity of the hilum lymph nodes with extension of the infection into the pericardial sac. (2) A hypersensitive response by the pericardium to an offending organism in which the immune reaction of

the body is inadequate. This parallels the present accepted explanation of a hypersensitive reaction on the part of the heart and serosal linings of the joints in the rheumatic fever state.

The latter concept seems more plausible because the pericardial fluid was sterile and nonpurulent in the five cases in which pericardiocentesis was performed. A virus as the cause is not seriously entertained in this series since the leucocyte counts ranged as high as 27,400 per cubic millimeter.

The reports of necropsy records concerning pericarditis reveal interesting figures relative to the incidence of the disease. Smith and Willius,⁵ reviewing 8,912 cases from the necropsy records of the Mayo Clinic, found 373 cases of pericarditis, or an incidence of 4.2 per cent from all causes. Seventy-one cases, or 49.3 per cent of 144 cases of adherent pericarditis, were of unknown etiology. They referred to the possibility that acute fibrinous pericarditis may take place as a result of an apparently trivial infection, which is not recognized at the time of occurrence and which may undergo spontaneous abatement, resulting in partial or complete obliteration of the pericardial sac. This is borne out by the fact that only 57 cases, or 39.5 per cent of their series, presented complaints that made the heart a major factor in the clinical picture. It is possible in the light of our series that an antecedent upper respiratory infection of mild or subclinical type may have been the etiological factor in some of their cases. Since in two of our cases a history of upper respiratory infection was not obtained, a subclinical antecedent carrier state may have existed, such as we now believe to be possible in many patients with rheumatic fever. If the preceding facts are true, clinical evaluation of mild or moderate precordial pain following in the wake of an acute upper respiratory infection takes on important clinical significance in that the symptoms may be due to a mild acute pericarditis.

Hard and fast conclusions cannot be made from this small series of cases, but it might be inferred that an antecedent upper respiratory infection without intrapulmonary disease may be an important predisposing cause of pericarditis with effusion.

SUMMARY

1. Eight cases of pericarditis with effusion following acute upper respiratory infection without intrathoracic disease are presented.

2. The relationship of acute upper respiratory infection of mild or subclinical type to partial or complete obliterative pericarditis found at autopsy is suggested.

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HEMIPLEGIA FOLLOWING CAROTID SINUS STIMULATION

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THE California Heart Association several years ago asked its members to pool their experiences in regard to untoward reactions from carotid sinus stimulation. Seven instances of hemiplegia which occurred immediately after carotid sinus stimulation were reported by members of the association. This communication, therefore, is submitted as a joint report.

Mechanical stimulation of the carotid sinus is now a common clinical diagnostic procedure and is accepted as a routine in complete neurological examinations. No serious untoward effects ordinarily occur. It is the purpose of this communication to describe these seven cases, to emphasize that this procedure is not always without danger, and to discuss the implications of the findings in relation to the mechanism of the carotid sinus reflex. In addition, several unusual, previously undescribed clinical manifestations of carotid sinus sensitivity are reported. One patient for years had had spontaneous, transient attacks of right-sided hemiplegia and dizziness. In this patient, right hemiplegia was reproduced by left carotid sinus stimulation. The preceding episodes of transient paralysis thus were a result, we believe, of spontaneous stimulation of the carotid sinus. Another patient suffered mental lapses, disorientation, and dizziness. These spontaneous attacks were duplicated by carotid sinus stimulation.

In September, 1941, Marmor and Sapirstein¹ reported the case of a patient who developed bilateral thrombosis of the anterior cerebral arteries following stimulation of a hypersensitive sinus. Levine² reported a single instance of hemiplegia after the procedure. The most complete study of hypersensitivity of the carotid sinus was done by Weiss and his collaborators.³ The clinical manifestations described were dizziness and syncope with or without convulsions. No instances of transient or persistent hemiplegia were described.

Ten instances of untoward response are reported in this study. Of these ten cases, only seven presented sufficient evidence to be certain that the hemiplegia was a direct result of mechanical stimulation of the carotid sinus. It is possible that in two other cases hemiplegia occurred as a direct result of the stimulation of the carotid sinus, but, in one (Case 8), twenty-four hours elapsed after stimulation before hemiplegia appeared, and in another, not reported here, the data were not sufficient.

The following members of the California Heart Association contributed material for this report: Louis E. Martin, Harold H. Rosenblum, Myron Prinzmetal, E. Richmond Ware, Lewis T. Bullock, Ferrall H. Moore, Lester S. Lipsitch, William C. Boeck, Donald J. Frick, Morris H. Nathanson, and Edward C. Rosenow. Miss Marjorie Edwards, Executive Secretary, assisted in compiling the data.

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TABLE I. PATIENTS WITH HEMIPLEGIA FOLLOWING CAROTID SINUS STIMULATION

CASE	SEX	AGE (YRS.)	BLOOD PRESSURE	DIAGNOSIS	COMPLAINTS	TYPE OF RESPONSE	CAROTID SINUS, PRESSURE	POSITION OF PATIENT	HEMIPLEGIA, SIDE, ONSET, DURATION
1	M	60	No data	Arteriosclerosis (retinal)	Dizziness, faintness, no loss of consciousness	Asystole, 15 seconds, B.P. 100/68	Moderate on right	Sitting	Left hemiplegia; onset immediate; duration 6 weeks
2	M	60	160/65	Syphilitic aortitis with aortic regurgitation	Dizzy spells	No asystole but bradycardia Asystole, 5 seconds, bradycardia 15 seconds	Very light on right Heavy on right	Recumbent	Left hemiplegia; onset 15 minutes after; duration 1 hour Left hemiplegia; onset immediate; duration 5 minutes
3	M	55	195/115	Arteriosclerosis, hypertension (old infarct)	Angina pectoris (severe)	Asystole, loss of consciousness	Light on right	Recumbent	Left hemiplegia (75% loss of strength); onset immediate; duration 2 weeks plus
4	M	54	No data	Arteriosclerosis, hypertension	Dizziness	Bradycardia, no loss of consciousness, faintness	Light on right	Recumbent	Left upper extremity; onset immediate; duration 1 day
5	M	53	153/100	Arteriosclerosis	Transient right hemiplegia, dizziness	No bradycardia or drop in B.P.	Light on left	Recumbent	Right hemiplegia; onset immediate; duration 1 week plus
6	F	42	No data	No data	Dizziness, headaches	No details	Chiropractic massage on right	Sitting	Left hemiplegia; onset immediate; duration 2 weeks plus
7	M	60	160/110	Arteriosclerosis	Syncopal attacks	Loss of consciousness	Moderate (side unknown)	Recumbent Sitting	Onset immediate; duration several months; complete recovery

CASE 1.—A white man, aged 60 years, a laborer, was admitted to the Los Angeles County General Hospital, complaining of dizziness and frequent attacks of faintness without loss of consciousness. These symptoms were precipitated by moving the head quickly from side to side, or by suddenly sitting up. He had experienced severe nausea but no vomiting or complete loss of consciousness. The physical examination showed a well-nourished and well-developed, florid man of sthenic habitus. No unusual sclerosis of the large arteries was noticed. The retinal arteries showed slight tortuosity and venous compression. Moderate pressure on the right carotid sinus was performed while the patient was sitting. This was not believed to be sufficient to obliterate the artery completely. The following note describes the succeeding events: Within approximately forty-five seconds the patient complained of dizziness. The pressure immediately was released. Ventricular standstill was noted for about fifteen seconds. He did not become unconscious at any time. Examination immediately afterward revealed the following significant findings: The patient was confused. There was left facial palsy. The left pupil was slightly larger than the right. Slight deviation of the tongue to the left was noted. There was flaccidity and weakness of the left arm and leg. The reflexes of the left upper extremity were absent. The left patellar reflex was hyperactive and the patient had a left positive Babinski reflex. Improvement in mentality began five days later when he was more alert, and on the next day some movement was noted in the left leg. Two weeks later some motor function was present in the left hand. He was generally stronger with increasing use of the left leg. Five weeks later he was walking about the ward, and on discharge, six weeks after the onset, there was only slight remaining weakness in the left arm and leg.

CASE 2.—A 60-year-old man, treated at the outpatient department of the Lane Hospital of the Stanford University School of Medicine in San Francisco, had syphilitic aortitis with aortic insufficiency and mild hypertension. He began to have dizzy spells while shaving. Right carotid sinus pressure produced some slowing of the heart with definite reproduction of the dizziness. Ten to fifteen minutes after carotid sinus stimulation, the patient was unable to walk and could not move the left arm or leg. There was no total paralysis. He was sent to the San Francisco City Hospital, where pressure on the right carotid sinus again caused temporary paralysis. After each stimulation the patient became numb and paralyzed on the left side. The paralysis disappeared after about fifteen minutes. There was a period of asystole for five seconds, followed by mild bradycardia for fifteen seconds.

CASE 3.—A 55-year-old man showed arteriosclerotic heart disease and angina pectoris following a probable myocardial infarction occurring two years previously. The right carotid sinus was massaged lightly while the patient was in the upright position. This was followed immediately by cardiac standstill and loss of consciousness for a few minutes. Slow recovery of consciousness occurred during the following fifteen to twenty minutes, at which time it was found that there was a weakness of the left hand and left leg, estimated at approximately 25 per cent of the strength of the opposite member. Recovery from the weakness of the left side was only partial when he was last seen approximately two weeks after the episode.

CASE 4.—The detailed findings of this case are not available, but hemiplegia occurred also in a man with hypertension and arteriosclerosis. Light pressure was applied over the right carotid sinus producing marked cardiac slowing followed by faintness, without loss of consciousness. Immediately afterward, marked weakness of the left upper extremity was observed. This disappeared the following day.

CASE 5.—A 53-year-old man complained of attacks of dizziness and syncope. The episodes were associated with double vision and impairment of coordination. On several occasions the right arm became weak and numb during the attacks. Frequently he was unable to talk during a seizure. The attacks were of abrupt onset. One morning he could not brush his teeth because of weakness and clumsiness of the right hand. The function of the right arm was gradually restored during the ensuing thirty minutes. These episodes had occurred frequently, and sometimes several times daily, from 1937 until he was first seen in 1941. They usually lasted about five minutes. After neurological examination it was thought that the patient had a psychoneurosis with transient hysterical paralysis of the right arm.

The blood pressure was 156/90. The attacks occurred occasionally on turning the head from one side to the other. The left carotid sinus was very lightly massaged. The stimulation was hardly begun when the patient stated that he felt dizzy and unsteady. There was no change in the heart rate. His face became congested, the eyes rolled, and the breathing was stertorous. He was laid immediately on the table, and his right arm fell limp to the side. There was complete paralysis of the right side. He was somewhat confused mentally but answered questions intelligently. There was no significant change in the blood pressure. After the administration of amyl nitrite, he felt better. After two hours the right leg recovered, but the right arm remained limp and helpless. Three and one-half hours later he was able to raise the right arm but could not flex the fingers. Neurological examination four days later revealed some weakness of the right eyelid and the muscles of the right forearm, and some weakness of the right angle of the mouth. The closing mechanism of the right eyelid appeared impaired. There was some weakness of the external and internal hamstrings of the right thigh. The right biceps, triceps, and supinator reflexes were slightly exaggerated, whereas those on the left were normal. The right patellar reflex was exaggerated. An intermittent positive Babinski sign was occasionally noted on the right. The patient was observed for several months following this stimulation, and he continued to have frequent attacks of the same character.

CASE 6.—A white woman, aged 42 years, developed a very severe headache on the top of the head following a cold. It was made worse by bending the neck. She had five chiropractic treatments for this headache. She stated that, during the last treatment, the chiropractor pressed rather firmly on the right side of her neck below the angle of the jaw, and immediately she became dizzy and faint but not unconscious, and then discovered that she could not move her left arm or left leg. Her husband entered the office and found her speaking incoherently and unable to walk. He had to carry her to the car. The left side of the face, the left arm, and the left leg were paralyzed, and she complained of numbness over the left side of the body. She was removed later to the Los Angeles Good Samaritan Hospital. There was no past history of symptoms referable to the cardiovascular system. The blood pressure measured 140/90. The neurological examination revealed the pupils to be equal, regular, and reacting to light and accommodation. There was a horizontal nystagmus when she looked in either direction. The movements of the left eye were slower than those of the right, but apparently there was no complete paralysis of any of the extraocular muscles. There was weakness of the left side of the face with hypertonicity on the right. The speech was thick at times, but there was no dysphagia or aphasia. There was only slight movement of the group of shoulder muscles on the left side, with almost complete paralysis of the left upper extremity. This arm was spastic with markedly exaggerated reflexes and pseudoclonus. Sensation was present on the left side but was slightly less than on the right. The knee could be lifted slightly on effort. There were exaggerated reflexes and pseudoclonus. There was a suggestive Babinski reaction on the left. The neurologist's impression was that "the history and findings are suggestive of cerebral thrombosis, secondary to manipulative procedures. An electroencephalogram might yield some information."

CASE 7.—A man, 60 years of age, had generalized arteriosclerosis and had had a very hypersensitive carotid sinus reflex with many rather severe syncopal attacks which could be induced by moderate pressure on either the right or left carotid sinus. The blood pressure was 160/110. Immediately following one induced attack, the patient developed a complete hemiplegia. He made a complete recovery from his hemiplegia although the symptoms lasted for several months. His syncopal attacks have been controlled fairly well by quite large doses of phenobarbital.

In the following case the hemiplegia cannot be ascribed definitely to carotid sinus pressure inasmuch as it occurred the day following the stimulation.

CASE 8.—A man, 72 years of age, complained of dizzy spells of several years' duration. He had moderate hypertension: his blood pressure was 170/100. There was no definite cardiac enlargement. General physical examination showed nothing abnormal. Pressure on

the right carotid sinus, made in the supine position, resulted in marked dizziness and cardiac arrest of several seconds' duration. When the patient assumed the erect position, he seemed very unsteady and complained of severe dizziness. He lay down for a short period but on leaving the office was still unsteady. The examination was performed in the morning, and the patient remained at home in the afternoon. He was still conscious of lessening degrees of dizziness. He slept well, and the following morning on awakening he found that he was unable to move his left arm and left lower extremity. The muscular weakness improved quite rapidly so that within two weeks he was able to be up and around. He was followed for about a year after this episode with no significant change in the clinical course.

OTHER CEREBRAL DISTURBANCES

Distressing cerebral complications, besides hemiplegia, have been reported several times. Weiss³ stated that he had observed but one patient with untoward symptoms. For several days following a spontaneous attack, one of his patients felt weak and exhausted. Moderate pressure on the sinus of this patient produced weakness, dizziness, and partial syncope in three to five seconds, and for several days thereafter she did not feel well. Two instances of cerebral irritability were reported in our series.

CASE 9.—A man, aged about 65 years, had arteriosclerosis and early senile dementia with mental lapses, disorientation, and dizziness. Pressure was made on the right carotid sinus. Asystole lasting about five seconds was produced. Following this he became very pale and was silent during the remainder of the office visit. His brother called the next day and stated that, following the pressure on the carotid sinus, his mental condition was much impaired for about twenty-four hours. He had remembered nothing and was completely disoriented.

CASE 10.—A robust Russian man, aged about 55 years, complained of dizzy spells. He gave a very clear history and seemed very rational. Pressure was applied on the right carotid sinus twice, once with the patient recumbent, and once with the patient upright. He acted peculiarly during the remainder of the examination. Following the examination, he was very excitable and extremely irrational. He drove his niece, a nurse, home. She stated that he was unable to drive safely and that they narrowly escaped several accidents. He acted very queerly at home, this condition lasting about thirty-six hours. He made a complete recovery but stated that the pressure on his neck made him feel "crazy." There was only slight bradycardia produced by pressing his sinus.

DISCUSSION

From an analysis of the first seven cases it is apparent that mechanical stimulation of the carotid sinus is not as innocuous as generally is believed, and it may be followed by more or less serious paralysis. The great majority of the patients were elderly and had arteriosclerosis and hypertension. The patients described by Marmor and Sapirstein¹ and by Levine² were also arteriosclerotic. It would appear, therefore, that, although stimulation of the carotid sinus may be harmless in young people, the procedure should be utilized with caution in elderly persons with arteriosclerosis.

The mechanism by which the paralysis occurs is worthy of comment. In six instances the right carotid sinus was stimulated and the paralysis was on the left side. In one instance, the left carotid sinus was massaged and the paralysis was on the right side. Thus it is clear that the paralysis is contralateral and the cerebral effect must be ipsilateral to the side of carotid sinus stimulation. It has been shown by Weiss³ that the cerebral ischemia following

pressure is not mechanical due to occlusion of the carotid artery. Furthermore, the hemiplegia in one patient (Case 5) abruptly followed light massage with very little pressure over the artery and with no change in the heart rate or blood pressure. The cerebral effect apparently is due to a direct unilateral cerebral action. Recent work by Engel and his co-workers⁴ offers additional evidence for this concept. They observed abnormalities of the electroencephalogram on the same side as the carotid sinus pressure in a patient with a direct cerebral reflex type of hypersensitive carotid sinus, that is, with no fall in blood pressure and no bradycardia. Interestingly, there occurred clonic spasms of the right arm and leg when the left cortex was affected by left carotid sinus pressure, and the left side reacted when the right carotid sinus was stimulated. Whether the abnormal cerebral waves are secondary to reflex vasoconstriction or are due to a direct cortical effect, is unknown. The usual concept of hemiplegia would suggest that the fundamental cerebral disturbance in our patients was due to ischemia brought about by reflex vasoconstriction of the ipsilateral side. A direct unilateral cerebral effect from carotid sinus pressure, therefore, would appear to be more important in our patients than the production of cardio-inhibition or vasodepression, inasmuch as the cerebral effect producing the paralysis always was localized on the side of the pressure. This is corroborated by the work of Galdston and his collaborators.⁵ They found that syncope and convulsions in certain patients would result from stimulation of the side that produced little or no bradycardia or drop in blood pressure, but that stimulation of the side which caused marked circulatory response would not produce these symptoms.

That the cerebral effect following carotid sinus pressure is not equally distributed bilaterally, but is predominantly ipsilateral, is suggested by many of the cases reported by Weiss.³ The initial convulsive twitchings, numbness, and tingling were always contralateral. In describing the patients whose symptoms arose presumably from a direct cerebral reflex, he said, "Depending on the degree and duration of pressure, the symptoms consisted of faintness and pallor of the face followed by unconsciousness, and, in most cases by convulsive twitchings which usually began on the contra-lateral side and became generalized. . . . Numbness and tingling of the extremities were prominent symptoms usually starting in the contra-lateral extremities and spreading to the whole body before actual fainting occurred." Even in Weiss' cases where syncope was produced by cardio-inhibition or a drop in blood pressure, there was often evidence of a predominating ipsilateral cerebral effect. The induction of such symptoms and signs as contralateral numbness, tingling, and convulsions of the extremities and ipsilateral numbness of the face, suggests a direct unilateral cerebral reflex mechanism, particularly since prolonged occlusion of the carotid artery below the sinus failed to induce any such symptoms. It is interesting, in view of the findings in our cases, that in none of his patients did the findings progress to hemiplegia.

It would appear that in many of the persons of the type described in this report there is advanced cerebral arteriosclerosis with great impairment of the blood supply to the brain. Whereas a temporary disturbance of the blood supply to a normal brain from carotid sinus stimulation would seem innocuous,

any further reduction of the blood flow in the brain with an already impaired blood supply may produce deleterious effects. This could explain the transient hemiplegia lasting only a few minutes. However, in the patients with more persistent hemiplegia following carotid sinus stimulation, a more permanent mechanism, either thrombosis or a small hemorrhage, would seem responsible. Thrombosis of the anterior cerebral arteries was observed by Marmor and Sapirstein.¹ In previous reports on carotid sinus sensitivity the predominant clinical manifestation described was dizziness and syncope, with or without convulsions. Stern⁶ described one case with gastrointestinal manifestations. Friedman⁷ reported two instances with anginal syndrome. In the present report are described two instances in which the patients had bizarre, previously undescribed manifestations, apparently due to spontaneous carotid sinus stimulation because they could be reproduced by carotid sinus pressure. One patient (Case 5), in addition to the dizziness and the other usual manifestations of carotid sinus sensitivity, had varying degrees of weakness of the right arm which was reproduced by carotid sinus stimulation. In another patient with marked cerebral arteriosclerosis and frequent episodes of loss of memory and disorientation (Case 9) stimulation of the carotid sinus produced a very severe attack lasting twenty-four hours. Thus, the additional cerebral ischemia induced by carotid sinus stimulation produced paralysis in the first patient, while, in the second patient, it enhanced the mental disturbances due to the cerebral ischemia of senility.

SUMMARY AND CONCLUSIONS

1. Seven instances of contralateral hemiplegia following carotid sinus pressure are reported.

2. Transient hemiplegia as a manifestation of hypersensitive carotid sinus activity is suggested by its reproduction in a patient who had had attacks for years.

3. Two patients were observed with mental aberration following carotid sinus pressure.

4. Carotid sinus pressure in the middle-aged or elderly arteriosclerotic patient may be productive of untoward results and should be applied cautiously.

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TRANSITORY A-V BLOCK OCCURRING DURING SCARLET FEVER

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THAT the heart may be involved in scarlet fever had been recognized for many years. Many reports and opinions have been recorded regarding the nature of the myocarditis occurring during the acute phase of this disease and the chronic valvular disorders which follow. Rosenbaum¹ reported 1,770 cases of scarlet fever, in 106 of which there were definite cardiac complications. A diagnosis of myocarditis was made in 88 of these cases, and was based upon clinical observations such as changes in heart rate, variation in the size of the heart, disturbances of conduction, et cetera. Swift,² in a treatise on the heart in infection, stated that cardiac complications occurred infrequently in scarlet fever, and he classified them as (1) toxic, (2) allergic, and (3) septicopycemic. The last two involve valvular damage. The, "toxic" manifestations, which are regarded as similar to those in diphtheria, are characterized by signs of cardiac weakness and are often accompanied by bradycardia. No mention of electrocardiographic changes was made.

Shookhoff and Taran³ reported 50 cases of scarlet fever in which electrocardiographic studies were made. Bradycardia was found in 25 per cent, but no lengthening of the P-R interval or other disturbances of conduction was observed. Place⁴ concluded that myocarditis in scarlet fever is very rare; he stated that since the use of the electrocardiogram "no well marked case (of myocarditis) has occurred in our wards in several thousand cases." Collaborating with Faulkner and Ohler, Place⁵ reported 171 cases in which electrocardiographic studies were made. Abnormal tracings were secured in 11, or 6 per cent. In five of the 11 the abnormality consisted merely of prolongation of the P-R interval beyond 0.2 second, and in six there were T-wave changes. The majority of these changes developed between the eighteenth and thirty-fourth days, and the degree of electrocardiographic abnormality was not influenced by the severity of the illness. Wickstrom⁶ observed prolongation of A-V conduction time beyond 0.2 second in five of a group of 100 patients. Schwarz⁷ studied 65 patients with scarlet fever clinically and electrocardiographically, and observed no electrocardiographic evidence of cardiac involvement. Berger and Olloz⁸ reported finding electrocardiographic evidence of myocarditis in four of a series of 66 cases, but mentioned no instance of complete heart block. Holz⁹ reported seven cases of scarlet fever, complicated by joint involvement, in which electrocardiographic evidence of conduction disturbance was found. In all of these cases the P-R interval was prolonged, and, in one case, partial block, with Wenckebach periods, was observed. Beer¹⁰ found electrocardiographic evidence

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of conduction disturbance in 14 cases of scarlet fever with joint involvement. Electrocardiographic abnormalities consisted of prolongation of the P-R interval or partial heart block. Roger¹¹ cited the case of a 21-year-old man whose heart rate dropped to 52 and stayed there for three days. He concluded that the focus of irritation was bulbar, because, under the influence of small doses of atropine, the heart rate rose to 64. Bernstein¹² reported the case of an 18-year-old boy who developed A-V dissociation after scarlet fever. Electrocardiographic studies were not made during the attack of scarlet fever, but a transient bradycardia was observed on the eighteenth day of the illness. Subsequently, this patient developed attacks of dizziness, blurred vision, dyspnea, and brief periods of unconsciousness. When he was re-examined about fourteen or fifteen months later, complete heart block and cardiac decompensation were observed.

Although no attempt was made to cover the literature, no mention of complete heart block occurring during scarlet fever was found. For this reason, and because of the difference of opinion regarding the nature of the myocardial involvement in this disease, two cases of complete heart block occurring during the course of scarlet fever are reported. Both were observed on the Medical Isolation service of the State University of Iowa Hospital in 1936.

CASE 1.—P. H. was born in 1918, and was considered a healthy infant. He had the usual diseases of childhood, but no scarlet fever, diphtheria, rheumatic fever, chorea, or frequent tonsillitis. There was no history of shortness of breath, heart consciousness, precordial pain, or syncope. About four days prior to admission to the hospital he complained of a slight head cold, general malaise, and fever. On the third day of his illness he noticed sore throat and hoarseness, and on the day of admission, flushing of the face and a diffuse rash over the chest.

Physical Examination.—The patient was a well-developed, well-nourished white man, 18 years of age. There was a punctate, erythematous rash which blanched on pressure and was most marked in the axillae and over the abdomen and thighs. The hearing and vision were normal. Ophthalmoscopic examination was negative. The teeth were in good condition. The tongue was coated on the dorsum and clear at the edges, where the papillae were prominent. The pharynx was very red, the pillars were edematous, and the tonsils were slightly enlarged. Small pin-point macules were present over the soft and hard palate. The lungs were normal to auscultation and percussion. The heart was of normal size, the rhythm was normal, and the sounds were of good quality. No murmurs were heard. The pulmonic second sound was slightly accentuated. The arterial blood pressure was 124/70. The abdomen, rectum, and extremities were normal. There were no abnormal neurological signs.

Laboratory Data.—The initial blood cell count showed 4,096,000 erythrocytes and 8,800 leucocytes, of which 78 per cent were polymorphonuclears, 17 per cent were lymphocytes, and 5 per cent were endothelial cells. The hemoglobin was 90 per cent (Sahli). The blood Wassermann reaction was negative. The urine was entirely normal on repeated examination. Throat cultures were negative for *Corynebacterium diphtheriae*, but positive for *Streptococcus hemolyticus*. The Dick test was negative, and the Schultz-Charlton reaction revealed a blanching of the rash over an area of 4 centimeters.

Subsequent Course.—At the time of admission the patient's temperature was 100° F., his heart rate was 86, and his respiratory rate was 18. He was given routine treatment, consisting of rest in bed, a high fluid intake, and a soft diet. No antitoxin was administered. His temperature was normal at the end of forty-eight hours and his angina was subsiding. The rash disappeared and desquamation started. He continued to be hoarse, and examination of the pharynx revealed chronic laryngitis with an acute exacerbation of the angina.

On the tenth and eleventh hospital days the temperature rose to 103° F. The only new observation at this time was tenderness of a cervical lymph node which subsided with local application of ice. On the fourteenth hospital day the temperature rose to 101.8° F. and, for the next ten days, fluctuated between normal and 103.6° F. The laryngitis became more severe. Blood cultures taken during this period showed no growth. The heart rate at first increased slightly with the rise in temperature. However, on January 31, the fifteenth hospital day and the nineteenth day of illness, the heart rate suddenly dropped to 40. Examination showed that the left border of the heart was a little outside the midclavicular line.

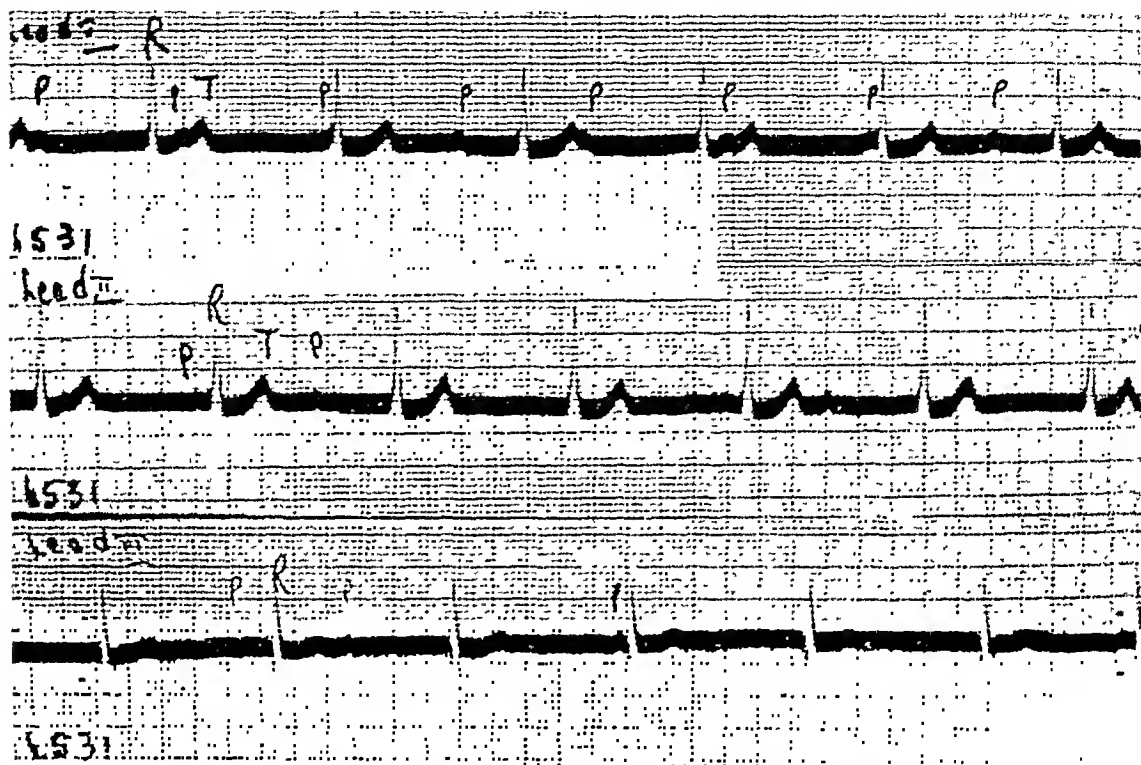


Fig. 1.—Case 1. P. H.: Electrocardiogram taken on the 15th hospital day, Jan. 31, 1936. This shows complete A-V block, the auricular rate being 80, the ventricular rate 56.

A systolic murmur was heard at the apex. The rhythm was regular except for an occasional pause; the pulmonic second sound was loud and rather snappy. The arterial blood pressure was 135/70. An electrocardiogram taken on this day showed complete heart block, with an auricular rate of 80, and a ventricular rate of 56, per minute. There was no associated dyspnea or heart consciousness. On the next day the same cardiac abnormalities were observed. On February 4 the cardiac rate was 80 per minute, and electrocardiographic study showed normal mechanism, with a P-R interval of 0.19 second, an inverted P₂, a large T₁ and T₂, and an isoelectric T₃. During the next week the cardiac rate varied between 60 and 90 per minute, but repeated electrocardiograms showed a normal mechanism. On February 6, the twenty-first hospital day and the twenty-fifth day of his illness, the patient developed pain in the shoulders and knees, without redness, swelling, or heat. He also had acute abdominal pain and a leucocytosis of 23,000. On the twenty-fourth hospital day the joint pain, abdominal pain, and laryngitis subsided; the temperature returned to normal and remained there. Daily examination of the urine for blood and albumin failed to reveal their presence. At the time the patient was discharged, on the forty-fifth hospital day, after almost three weeks of normal temperature, the heart rate was 70, the heart was of normal size, the systolic murmur had disappeared, and the pulmonic second sound was no longer loud and snappy. An electrocardiogram shortly before the time of discharge showed a P-R interval of 0.14 second.

The patient returned to the hospital June 23, 1936, for re-examination. After returning home he had remained in bed for one month, and, following this, had restricted his exercise. He had had no symptoms referable to the nasopharynx or the cardiovascular system. His appetite had remained good and he had gained 10 pounds in weight. Throughout this time he had been afebrile and his heart rate had varied between 60 and 80 per minute. Physical examination was essentially negative. The heart was of normal size, the rhythm was normal, no murmurs were heard, and the pulmonic second sound was somewhat accentuated. The arterial blood pressure was 160/100. The urine was normal. An electrocardiogram showed normal mechanism; the P-R interval was normal, and there was no abnormal deviation of the electrical axis. This patient returned for re-examination regularly throughout the next two years. At no time did the history indicate cardiac involvement; examination of the heart was negative and electrocardiographic studies were normal. He has been in the Army for the past three years and is now a captain in the Air Corps on active combat duty in the Southwest Pacific area.

CASE 2.—R. G., according to his history, gave no evidence of any cardiac involvement prior to Jan. 15, 1936, when he was admitted to the hospital during an attack of scarlet fever. He was born in 1916 and had been considered a healthy infant. He had had the usual diseases of childhood, but no scarlet fever, diphtheria, rheumatic fever, chorea, or frequent tonsillitis. There was no history of heart consciousness, precordial pain, shortness of breath, or syncope. In 1926 he developed gonorrheal ophthalmitis on the right and secondary glaucoma. Two days before admission he noticed a slight sore throat and some fatigue. The following day his throat was quite painful and he had a rash over his abdomen. He was admitted on the third day of his illness.

Physical Examination.—The patient was a well-developed, well-nourished white man, aged 20 years. There was a diffuse, punctate rash which was most prominent over the chest and abdomen. Hearing was unimpaired, but there was loss of vision and corneal opacity on the right. The teeth were normal. The tongue was coated with a grayish exudate, and the papillae at the margins were hypertrophied. The oropharynx was red, and there were pinpoint macules over the soft and hard palates. A few cervical lymph nodes were palpable. The thyroid was not enlarged. Examination of the chest was negative. The heart was normal in size, the rhythm was regular, and no murmurs were heard. The arterial blood pressure was 130/80. The abdomen, rectum, and extremities were essentially normal. No abnormal neurological signs were elicited.

Laboratory Data.—At the time of admission the blood cell count showed 4,650,000 erythrocytes and 20,200 leucocytes, of which 87 per cent were polymorphonuclears and 13 per cent lymphocytes. The hemoglobin was 90 per cent (Sahli). Repeated urine examinations were negative. The blood Wassermann reaction was negative. Throat cultures were negative for *Corynebacterium diphtheriae*, but positive for *Streptococcus hemolyticus*. The Dick test was negative. The Schultz-Charlton reaction showed a large area of selective blanching.

Subsequent Course.—On admission this patient had a temperature of 101° F., a heart rate of 110, and a respiratory rate of 23 per minute. His temperature fluctuated between normal and 100° F. for the following eleven days, and then became normal. Treatment was mainly symptomatic and supportive, and consisted of rest in bed, a high fluid intake, and a soft diet. Antitoxin was not given. Throughout this time the patient was without complaint and in good spirits; the angina cleared up, the rash disappeared, and desquamation began. On the morning of the eighteenth hospital day and the twenty-first day of illness, there was an unexplained rise in temperature to 101.4° F. On January 31, the nineteenth hospital day, the patient suddenly complained of marked weakness. The pulse rate was recorded by the nurse as 38 per minute. He was examined shortly after the onset of the weakness and was found to be pale and perspiring profusely. He complained of some nausea and weakness, but there was no heart consciousness, cardiac pain, dyspnea, or cyanosis. The patient stated that he felt as if he were "floating away." The cardiac and radial pulse rates were 26, and the rhythm was slightly irregular. The heart was normal in size, the sounds were of good quality, and no murmurs were heard. Electrocardiographic study on the same day showed

complete A-V dissociation, with an auricular rate of 107 and a ventricular rate of 25 per minute, and with ventricular standstill up to five seconds.

The patient continued to complain of some weakness and nausea during the following forty-eight hours, but developed no other complaints. He was afebrile during the remainder of his hospital stay except for rises of temperature to 99.8° F. on the twenty-first and twenty-second hospital days. Electrocardiographic studies were made once or twice a day. On February 1, the twentieth hospital day, partial A-V heart block was present. This persisted until February 4, when simple prolongation of the P-R interval with dropped beats was observed. The P-R interval varied between 0.32 and 0.41 second. This type of curve was obtained until February 11, the thirtieth hospital day, when normal mechanism, with a P-R interval of 0.16 and ventricular rate of 62, was present. The T waves, which had been biphasic, were now upright in all leads. From this time until the day of discharge, Feb. 21, 1936, the electrocardiograms were normal.



Fig. 2.—Case 2. R. G.: Electrocardiogram taken on the 19th hospital day, Jan. 31, 1936. The auricular rate was 107; the ventricular rate was 25. Note long periods of ventricular asystole.

The patient returned for re-examination June 17, 1936. For one month after discharge from the hospital he had remained in bed, and for the following three months he had been on very restricted exercise. He had had no nasopharyngeal or cardiovascular symptoms. His temperature had been observed daily and had been normal throughout the entire period. His heart rate had varied between 70 and 96 per minute. He had gained 20 pounds. Physical examination was entirely negative. The heart was of normal size, and the rhythm regular. No murmurs were heard. The arterial blood pressure was 110/82. The urine was normal. The electrocardiogram was normal.

This patient has been examined repeatedly throughout the past nine years. He was last seen on April 26, 1945, at which time the history was essentially negative; physical examination was negative except for the glass eye on the right. The loss of this eye alone has blocked his induction into the Army on six occasions. He has passed examinations for life insurance, works as a chiropodist, and has had but four weeks' vacation during the past nine years. The electrocardiogram, including Lead IV F, was entirely normal. The three standard leads could be superimposed on the curve taken at the time he left the hospital in February, 1936.

Because the manifestations of the acute and late phases of cardiac involvement in scarlet fever are analogous to those of rheumatic fever, many authorities have postulated that the cardiac complications which occur during the acute stage or following upon scarlet fever indicate part of a rheumatic cycle. Conduction disturbances are considered to be relatively common during acute rheumatic fever, and have occurred during other acute infectious diseases. Rosenberg¹³ recently reported two cases of epidemic parotitis accompanied by temporary electrocardiographic evidence of complete heart block. In most of these cases the disturbance in conduction proved to be transitory, and, as far as was ascertained, no evidence of residual cardiac involvement could be found. Unfortunately, these patients were not observed for any length of time after the initial illness.

Many investigators have described microscopic focal myocardial lesions in scarlet fever resembling those found in rheumatic fever. Fahr^{14, 15} examined one series of nine and another of eleven postscarlatinal hearts. Small collections of round cells were common, but he believed he could differentiate them from Aschoff nodules. Schmorl (cited by Fahr¹⁴) described myocardial "rheumatic nodules" in a child who died of scarlet fever and had no previous history of rheumatism. Gross and Ehrlich¹⁶ point out that the true Aschoff nodule does not attain its specific characteristics until after six weeks or more.

Although such lesions may be responsible for the chronic endocarditis and myocarditis which follow scarlet fever, they cannot be offered as a satisfactory explanation for the transitory cardiac murmurs and conduction disturbances which appear during the acute or early convalescent stages of the disease. These latter changes have been considered as manifestations of actual, although temporary, myocardial damage of the so-called toxic type.

Krauss¹⁷ reported two cases of sudden death on the sixth and seventh days, respectively, of scarlet fever. At autopsy the heart was dilated and flabby, and infiltrations of round cells were present. Similar cases have been observed by Goldschmidt¹⁸ and Gouget and Dechaux.¹⁹ The latter authors cited over fourteen cases of sudden death occurring at various stages of the disease. They concluded that there is usually no pathologic change which would account for death, and suggested that the deaths occurring at the beginning of the disease resulted from massive intoxication of the whole central nervous system, whereas those which followed the usual course of the disease could be accounted for by the theory that "the condition of the nerve cells had been modified in some obscure way by the action of toxins, so that even a slight incidental cause, by producing in their neighborhood some abnormal stimulus, suffices to produce sudden or rapid death." The possibility of myocarditis or suprarenal lesions were also considered, but no mention of suprarenal lesions, especially hemorrhage, in scarlet fever could be found.

Weill and Mouriquand²⁰ reported a case of sudden death on the thirteenth day after onset of scarlet fever. At necropsy a soft, yellow-red, but otherwise normal, heart was found. Microscopic study revealed perivascular and interstitial round cell infiltration and fragmentation of the muscle fibers. These observations agree with those cited by earlier workers. Virchow²¹ observed eight

hearts after death from scarlet fever, and found only a beginning fatty infiltration. In 1882, Litten²² described the heart in the early stages as flabby and anemic, and, in cases of longer duration, as yellowish, with loss of cross-striations and the presence of fat droplets. Ott²³ reported the following post-mortem observations in the case of a 7-year-old boy who died of scarlet fever nephritis: the left ventricle was much enlarged, the muscle fibers were unchanged, there was a slight amount of round cell infiltration in the interstitial tissue, and the ganglion cells showed fine, granular degeneration of the protoplasm, solution of the nucleus, and pericellular edema. Romberg,²⁴ in 1891, examined the hearts of ten persons who died of scarlet fever, found parenchymal degeneration of muscle fibers and interstitial round cell infiltration, and stated that the heart ganglia were not remarkable. Aschoff,²⁵ in 1906, described five cases, in one of which there was infiltration of plasma cells subendocardially; in the others no parenchymal degeneration was found. The heart nerve centers were not examined. Selinoff,²⁶ in 1913, found that the pathologic changes in the ganglion cells were more marked than those in the heart muscle in a series of twelve cases. He stated that the myocardium suffers chiefly parenchymal degeneration, whereas one finds collapse of the Nissl bodies, vacuolar degeneration, and necrotic changes in the nerve cells.

Stegemann,²⁷ in 1914, examined 49 patients with scarlet fever, who ranged in age from 6 months to 12 years, in special reference to the heart ganglia. He divided these cases into three groups, depending upon the day of illness on which death occurred. Eighteen died before the fifth day. In these "severely toxic cases of short duration," the parenchymatous changes in the myocardium were not marked. With the "infectious form of long duration," acute parenchymous degeneration, fatty infiltration, and necrosis were seen. Interstitial round cell infiltration of the heart wall was absent in the former but present in the latter. Round cell infiltration in the stroma of the ganglia, fatty infiltration, and necrosis of the nerve cells, more marked in the severely toxic cases, were found as early as the first day. In all of the cases there were definite changes in the cardiac ganglia in the form of cellular accumulation in the stroma of the ganglion cells. Recently the existence of a conduction system in the heart has been questioned.²⁸ Nonidez²⁹ has demonstrated definite sinoauricular and auriculoventricular nodes, and main, right, and left bundles in the *Rhesus* monkey and dog. He also showed that the nodes are supplied by axons of neurons of the intrinsic cardiac ganglia.

In marked contrast to rheumatic fever and diphtheria, serious cardiac complications in scarlet fever are uncommon, and their occurrence seems to be a matter of chance. In spite of this fact, many hypotheses as to the mechanism of their production have been postulated, and much evidence has been accumulated in support of the various theories. The two cases of heart block reported above appear to be similar to those seen during mumps by Rosenberg; all occurred fairly early during the illness, without other evidence of cardiac involvement, and were transitory; they were due, in all probability, to toxic changes. Edema or early round cell infiltration with impingement on the conduction system could cause a temporary, but complete, A-V dissociation. Coincidence will account for

the fact that these two patients, unrelated and coming from widely separated towns developed the only complete heart block during scarlet fever to be recorded in recent literature on the same day and in the same room, within a few hours of one another.

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THE RATE AND CONTROL OF THE BLOOD FLOW THROUGH THE SKIN OF THE LOWER EXTREMITIES

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INTRODUCTION

MOST of our earlier published investigations concerning the control and rate of the blood flow through the skin were limited to the upper extremities.^{20, 21, 23} Evidence presented by various authors,^{11, 32, 37, 39, 45} however, goes to show that there are differences between the vasomotor responses of the vessels of the lower and upper extremities which, in man, as suggested by Pickering and Hess,³⁷ may be the result of the assumption of the upright posture. The vessels of the toes not only seem more susceptible to constrictor influences than those of the fingers,³⁹ but they are also relatively refractory to vasodilating agents.^{5, 26}

This paper is, therefore, devoted to investigations of the rate and control of the blood flow through the skin of the toes. Apart from purely physiological considerations, accurate knowledge of the latter is essential both for diagnosis and evaluation of changes in the blood flow following therapeutic measures in peripheral vascular diseases. There occurs also a higher incidence of chronic occlusive arterial disease in the lower extremities than in the upper extremities which, in the light of the above data, may be of considerable significance.

The methods generally used for measuring tone and function of the blood vessels, like skin temperature and calorimetric readings, furnish either indirect indices of the blood flow only, or, as in the case of the oscillometric index, they do not deal with the peripheral circulation in a strict sense. For quantitative measurement of the blood flow, plethysmography has to be resorted to, and the number of different foot plethysmographs evolved during recent years^{3, 12, 14, 25, 42, 50} indicates clearly the need for such methods. As pointed out in earlier papers, the results obtained with any limb plethysmograph necessarily refer to both the muscle and the skin enclosed within the instrument. Therefore, ambiguity will arise because the vessels supplying the skin do not respond necessarily in the same way to the same drug or stimulus as do the vessels supplying the muscle (often they react antagonistically^{10, 16, 24, 31, 38, 40, 48}), nor need they be affected to the same degree by the pathologic process.

Also, even if the results obtained with limb plethysmographs were referable to skin only, their evaluation would be rendered difficult by the fact that, on account of anatomic differences in the arterial tree, the blood flow through the

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various skin areas enclosed cannot be expected to be uniform. Indeed investigations by various authors^{1, 13, 23} demonstrate that "observations on the blood flow and vascular reactions in one skin area cannot necessarily be applied to others at the periphery."¹³ Our optical finger plethysmograph was, therefore, adapted for investigations of the blood flow through the toes. The results obtained are not only strictly referable to the blood flow through the skin but they are also representative of the *ultimate* circulation, in contrast to the oscillometer, which deals with the *penultimate* circulation only.*

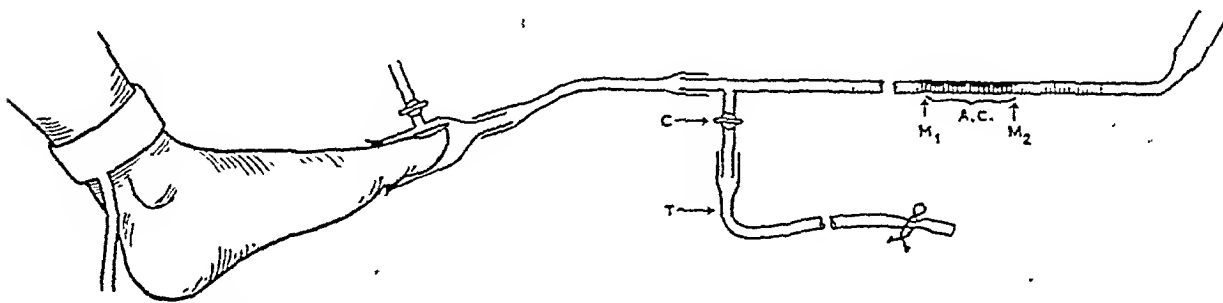


Fig. 1.—Toe plethysmograph as used for optical recording of the blood flow (for description see text).

METHODS AND MATERIAL

The methods used in this study follow closely those previously described,^{21, 23} and for details the reader is referred to the preceding papers. Continuous volume records of the toes were obtained (Fig. 1) by enclosing a toe within a glass plethysmograph which was connected to a pipette graduated in 0.01 c.c. and containing a column of alcohol (A.C. in Fig. 1). When the plethysmograph was sealed with petrolatum and the taps were closed, the volume changes of the toes were transmitted to the alcohol column, the movements of which were enlarged and projected onto the paper of a recording camera, as previously described.²¹ Registration was effected by the meniscus of the alcohol column (M_1 or M_2) which cast a shadow upon the photographic paper.²¹ This arrangement is capable of exact and undistorted measurement of the changes in skin volume, differences of 0.001 c.c. being easily recorded. Whatever the enlargement, no calibration is required since the graduation of the pipette appears as white horizontal lines on the film, effecting automatic calibration of the system. Knowing that changes in respiration cause peripheral reflex constriction,^{6, 19, 20} the respiratory movements were, as a rule, simultaneously recorded. In addition, the skin temperature of one or more toes next to the one measured plethysmographically was recorded simultaneously by means of thermocouples, and the pulsations of the dorsalis pedis arteries were registered by means of a Frank's capsule in many subjects (e.g., Figs. 6, 4, and 23).

We have been using these methods since 1932 for both physiologic investigations and routine clinical tests, and the results communicated herein refer to tests carried out on more than two thousand subjects.

The observations were conducted in a draft-free and noiseless room and, unless otherwise stated, refer to "warm-handed" subjects who had normal cardiovascular systems. The room temperature was kept constant during the experiments. No effort was made to control the relative humidity, which has little effect on the dissipation of heat from the body at the room temperature used in this study.^{39, 46} All the tests were performed after thirty to sixty minutes' rest. The subjects were, unless otherwise stated, resting comfortably in a type of Gatch bed, with the hips and knees flexed at about 60 degrees and the head and

*The terms *ultimate* circulation and *penultimate* circulation as used in this sense have been suggested by Professor C. F. M. Saint.

shoulders slightly elevated. Additional investigations were carried out with the legs elevated to about 45 degrees to study the effect of changes in posture upon the blood flow. Reflex dilatation of the vessels of the toes was obtained by immersion of one upper limb into water of 45° C. and covering the subject with blankets to prevent the dissipation of heat.

RESULTS

A. The Plethysmogram of the Toes During Rest.—The method is sensitive enough to register readily the blood flow even of a small toe in all its detail. This is of clinical importance since pathologic processes may either pick out a single digital artery or affect them all in varying degrees. In the case of the toes, particularly the big toe, the plethysmograph necessarily is sealed just proximal to the interphalangeal joint. It therefore encloses skin covering mainly the end phalanx. The latter, however, contains a vast amount of arteriovenous anastomoses, and thus has a considerably greater blood flow than the skin of the proximal phalanges which show only a few of these structures. Thus, strictly speaking, the plethysmogram of the big toe can be compared with that of the finger tip only.

1. The Height of the Pulse Volume: All other factors being equal, the height of the pulse volume depends upon the amount of tissue enclosed within the plethysmograph. Therefore differences in the height of the pulse volume must be expected in various subjects and, for this reason, the recorded height of the pulse volume is not a strictly comparable index of the circulation. Comparable indices are, however, easily obtained by correcting the height of the pulse volume to a mean digital volume (conveniently 15 c.c.) by means of the simple formula:

$$\text{Pulse volume (corrected)} = \frac{\text{Pulse volume (recorded)} \times 15}{\text{Digital volume in cubic centimeters}}$$

Thus, the corrected pulse volume of a very big first toe of 30 c.c. tissue volume which records a pulse volume of 0.04 c.c. is the same as that of a small toe of 7.5 c.c. which records a pulse volume of only 0.01 c.c., i.e., 0.02 cubic centimeters. While this is the correct procedure, it complicates the issue. For all practical purposes, however, it is sufficient, according to my experience, to compare the uncorrected height of the pulse volume of respective toes in various subjects if the above point is kept in mind. Therefore all our values refer to the uncorrected pulse volume of the big toe unless otherwise stated.

Fig. 2.—The pulse volume of a normal subject at various states of vasomotor tone. *A*, Moderately constricted, first left toe; skin temperature, 26° C. *B*, Moderately dilated, first left toe; skin temperature, 30° C. *C*, Fully dilated, first left toe; skin temperature, 35° C. *D*, Fully dilated, second left toe; skin temperature, 34.3° C. Room temperature, 21° C. Reduction of original tracings to two-thirds.

All tracings were obtained in reclining position unless otherwise stated, and in all the following abbreviations have been used:

P = pressure in cuff during venous congestion test; *P.V.* = pulse volume; *R* = respiratory movements (arrow indicates inspiration); *S* = signal; *S.G.* = sphygmogram of arteria dorsalis pedis; *SK.T.* = skin temperature; ordinates in all tracings = two seconds; white horizontal line = calibration for pulse volume and digital volume. Change from line to line equals 0.01 cubic centimeter.

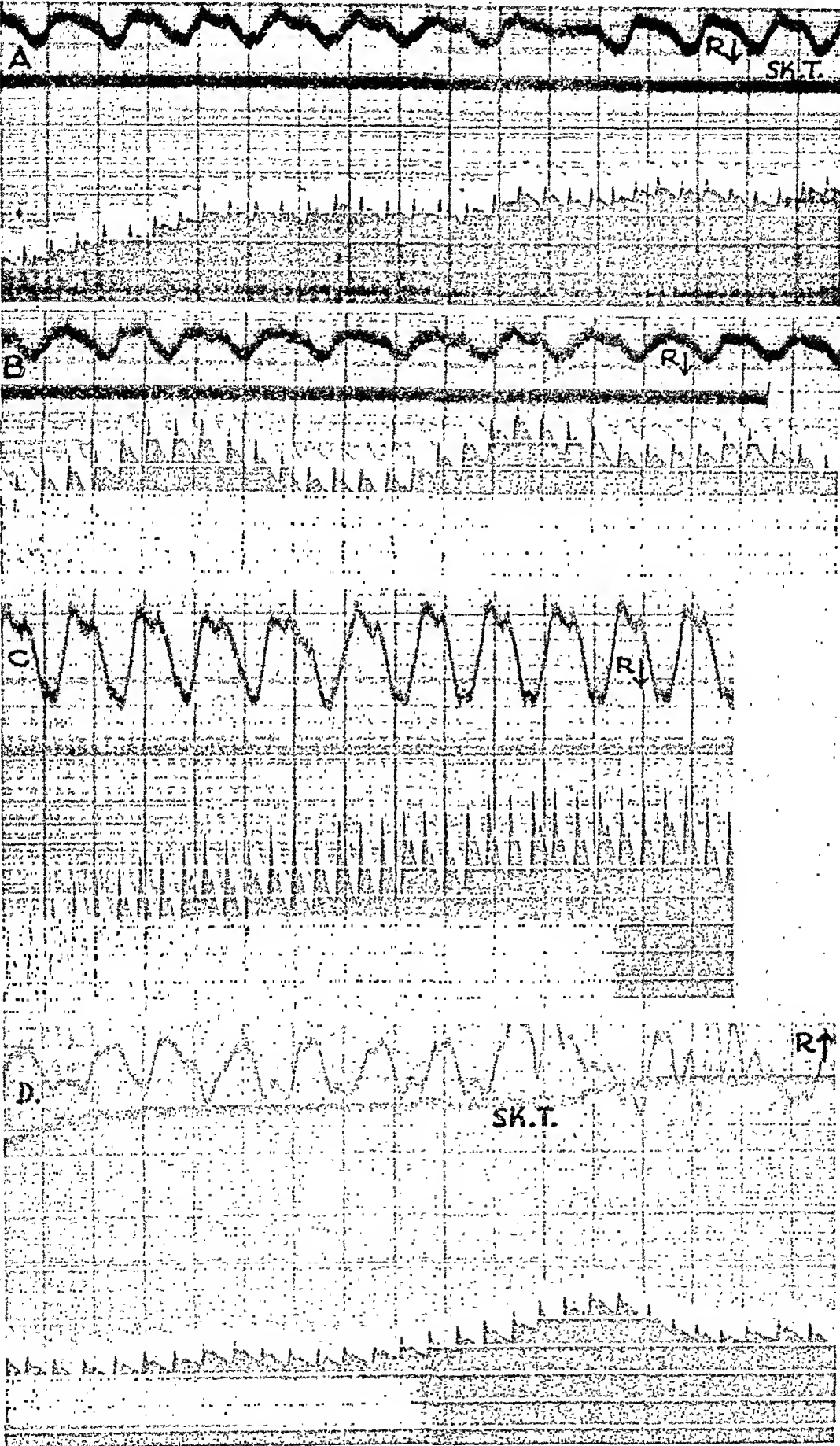


Fig. 2.—(For legend see opposite page.)

The height of the pulse volume in a normal subject is dependent upon the vasomotor tone (Figs. 2 and 10). As a rule it varies between 0.002 c.c. during maximum constriction and 0.025 c.c. during full dilatation. Occasionally, in younger subjects, values up to 0.045 c.c. are met with, while in others, particularly older subjects without clinical signs of arterial disease, the pulse volume during full dilatation may not exceed 0.020 cubic centimeters. Due to the smaller amount of tissue enclosed, the recorded pulse volume of a small toe reaches about 0.01 c.c. only during full dilatation (Fig. 2, D).

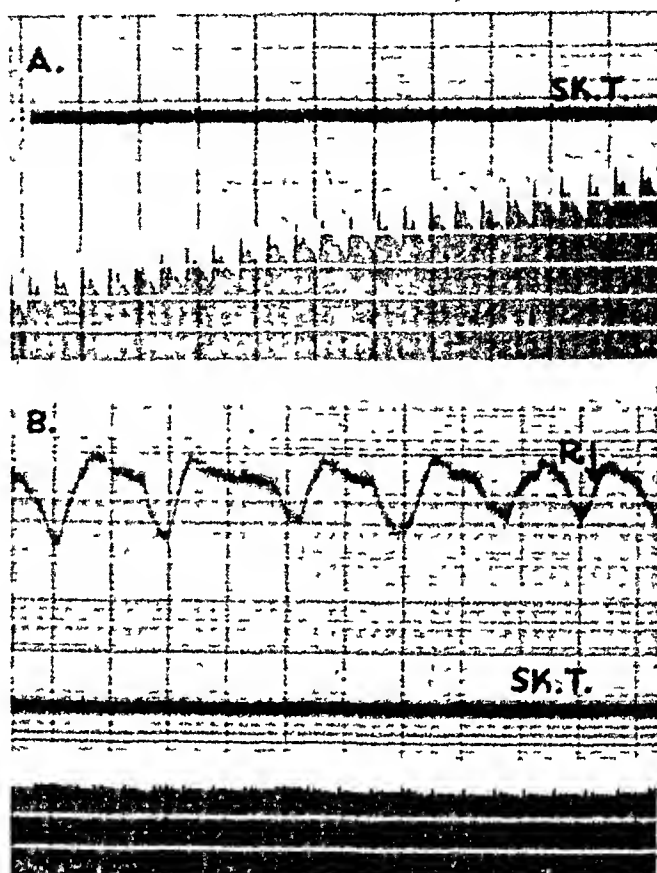


Fig. 3.—Pulse volume of a normal subject demonstrating difference between vasomotor tone of upper and lower extremities. A, Third left finger showing moderate dilatation. Skin temperature, 31° C. B, First left toe, taken immediately afterwards but showing full constriction. Skin temperature 23° C. Room temperature 22° C. For abbreviations, consult legend to Fig. 2. Reduction of original tracings to two-thirds.

As previously indicated²² the vessels of the fingers under basal conditions and at room temperatures of 20° to 23° C. are usually neither constricted nor fully dilated but assume a value intermediate between these extremes, allowing adjustment according to the needs of body temperature regulation. The pulse volume of the toes in the same subjects, however, is as a rule found near the lower limit of normality under similar circumstances, the vessels often being actually maximally constricted even in "warm-handed" subjects (Fig. 3). This indicates that the vasomotor tone of the blood vessels of the lower extremities is considerably higher than that of the fingers. In "cold-handed" subjects

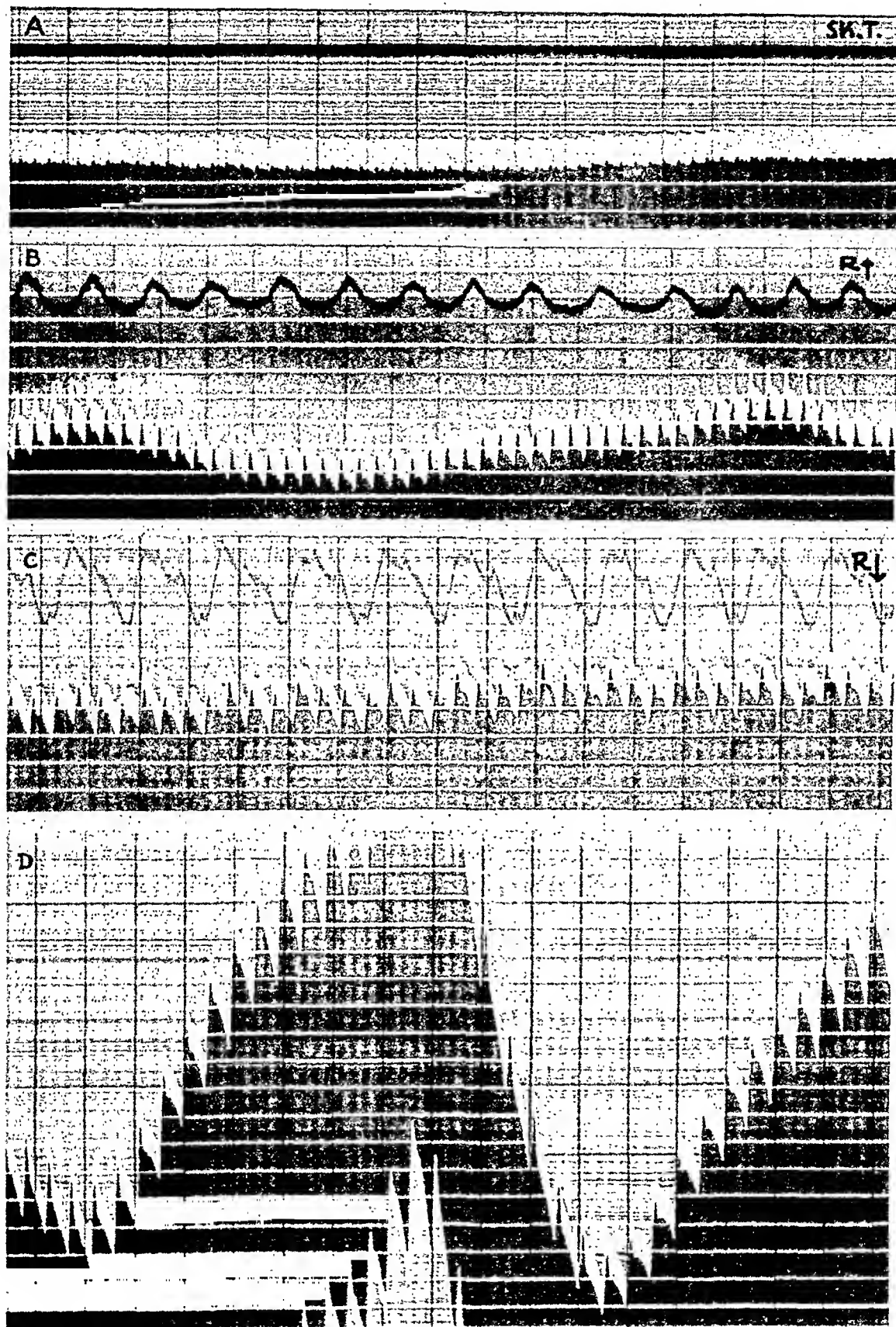


Fig. 4.—Spontaneous fluctuations in pulse and digital volume. A, Normal subject (first left toe) during rest. High vasomotor tone. Skin temperature 22.8°C . B, Normal subject (first left toe) moderately dilated. Skin temperature 31°C . C, Absence of spontaneous fluctuations following lumbar ganglionectomy (first right toe). Skin temperature 34°C . D, Normal subject fully dilated but elevated (first left toe). Skin temperature 34.5°C . Reduction of original tracings to two-thirds. Room temperature 23°C . For abbreviations, etc., consult legend to Fig. 2.

without clinical signs of arterial disease, the vessels, when tested under the same conditions, are invariably fully constricted, the pulse volume being rarely higher than 0.002 cubic centimeter.

2. **Fluctuations in the Height of the Pulse Volume:** The height of the pulse volume of the fingers has been found to be in a state of continuous rhythmic fluctuation which is abolished by the interruption of the sympathetic pathways (Goetz²³). It therefore reflects the rhythmic fluctuating nature of sympathetic activity. Indeed, the pulse volume is an exquisite indicator of that vasomotor activity which is of insufficient degree to show itself in blood pressure changes. However, in the lower extremities during rest these fluctuations of the pulse volume are either absent or very shallow (Fig. 4, *A*) on account of the high vasomotor tone just demonstrated. As the vasomotor tone of the toe vessels diminishes during body heating and the pulse volume rises, fluctuations become registrable (Fig. 4, *B*). They are extremely prominent in the elevated limb but shallow during dependency, which is particularly obvious during full dilatation when, in the elevated limb, the fluctuations are at their maximum (Fig. 4, *D*).

Naturally, the plethysmogram reflects all known variations in shape and rhythm of the sphygmogram. A Corrigan or water-hammer pulse, pulsus alternans, pulsus bigeminus, arrhythmias, and the like, are easily demonstrated (Fig. 5). Of particular interest are the changes in the pattern demonstrated in Fig. 5, *D*, which are due to changes in the character of the blood pressure occurring during artificially induced hypoglycemic shock. As is well known, the blood and pulse pressures rise during hypoglycemia; this is well reflected in the changes in the pattern of the pulse volume, particularly in the disappearance of the dierotic wave.

3. **Fluctuations in Digital Volume:** The plethysmogram does not, as a rule, move along a straight line but fluctuations occur which indicate changes in toe volume (Fig. 4). These volume changes correspond to, and are mainly the result of, fluctuations in the height of the pulse volume. Consequently, spontaneous changes in digital volume are less prominent in the toes than in the fingers on account of the higher vasomotor tone in the former (Fig. 4, *A*), but they become equally marked as the vasomotor tone is relaxed (Fig. 4, *B*). These changes assume considerable proportions in the elevated limb (Fig. 4, *D*) and are very less marked during dependency. Like the changes in pulse volume, they are dependent upon the integrity of the sympathetic nervous system and therefore are absent following ganglionectomy (Fig. 4, *C*).

Abramson and Katzenstein,² using their foot plethysmograph, reported that spontaneous fluctuations in blood flow were characteristic for the hand, but in

Fig. 5.—Changes in shape and rhythm of pulse volume. *A*, In auricular fibrillation (first left toe). Skin temperature 32° C. *B*, Interpolated extra systoles (first right toe). Skin temperature 31.3° C. *C*, Dropped beats (first left toe). Fully dilated. Skin temperature 33° C. *D*, Change in shape with change in blood pressure (first left toe). (a) During rest. B. P. 116/75. Skin temperature 36° C. (b) During artificial hypoglycemia. B. P. 156/56. Skin temperature 36° C. *E*, Pulsus bigeminus (first right toe). Skin temperature 33.7° C. Reduction of original tracings to two-thirds. Room temperature 22° C. For abbreviations, etc., consult legend to Fig. 2.

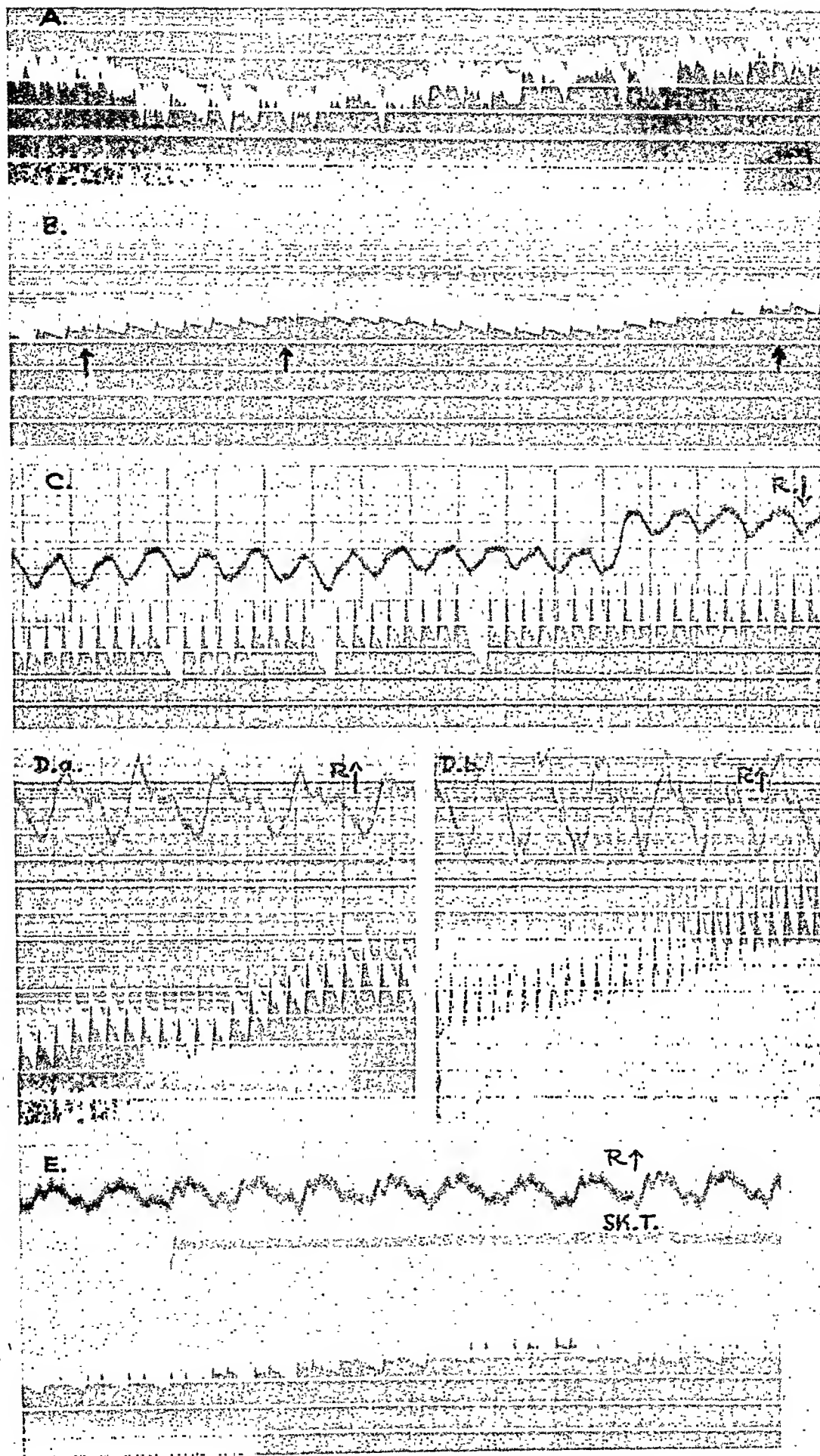


Fig. 5.—(For legend see opposite page.)

the foot they were either "absent or insignificant." Obviously in these authors' experiments the feet, in contrast to the hands, were tested during dependency, which, in the light of the above data, easily explains their failure to demonstrate spontaneous fluctuations. There can be no doubt from our investigations that, in the lower extremities, spontaneous fluctuations do occur in the same degree as in the upper extremities, if tested under identical conditions, which include identical hemostatic conditions as expressed by posture.

Spontaneous fluctuations in the toe volume are less pronounced during the venous congestion which is obtained from inflating to 60 mm. Hg a cuff fixed at the ankle. Nevertheless, they are still obtained (Fig. 8, *B*). This is evidence that the fluctuations are mainly the result of changes in arterial inflow since, according to Lewis,³³ both veins and capillaries are unable to constrict against the pressure used.

Ever since the first description of plethysmographs, changes occurring simultaneously with the respiration have been described, the true vasomotor nature of which has been maintained by some and doubted by others. Unless there was pronounced cardiac respiratory arrhythmia, changes in the toe volume resulting from the normal respiration were hardly ever prominent in our tracings.

In our earlier communications we described how a single deep inspiration, imitative of a sigh, or a series of deep breaths regularly produced peripheral constriction in the fingers, the degree depending upon the tone of the digital vessels.^{19, 20} This fact since has been amply confirmed by numerous authors. The vessels of the toes are affected by this constriction to the same degree (Fig. 6, *A*), and the reaction shows all the characteristics described elsewhere.^{20, 23} This constriction is set in train only by the inspiratory phase, and since it is not obtained following lumbar ganglionectomy (Fig. 6, *D*) it is dependent upon the integrity of the sympathetic pathways and is thus a true vasoconstrictor reflex. When moderately or fully dilated the reaction is easily recorded, but under ordinary conditions the reaction may be absent because of the already high vasomotor tone. Indeed, even a slight increase may be obtained instead of the usual fall (Fig. 6, *B*). Thus Peters,²⁵ using our method, did not obtain vasoconstriction in the one subject tested by him. His Fig. 12 is strikingly similar to our Fig. 6, *B*. The decrease in digital volume following a deep breath is extremely pronounced in the elevated leg when the venous plexus is empty and well drained (Fig. 6, *C*). Under such conditions constriction of the veins could hardly account for such a marked volume decrease. The constrictor reflex following a deep breath affects therefore mainly, if not solely, the arteries.

The effects of various sensory stimuli (e.g., an unexpected noise [Fig. 7, *A*], application of cold or pain, single or multiple principles, emotional content of thought or mental strain [Fig. 7, *B*], or the anticipation of any of these) upon the peripheral circulation were tested and they always resulted in vasoconstriction. All of these are well-known vasoconstrictor reflexes and as such are not obtained after ganglionectomy (Fig. 7, *C*). A similar con-

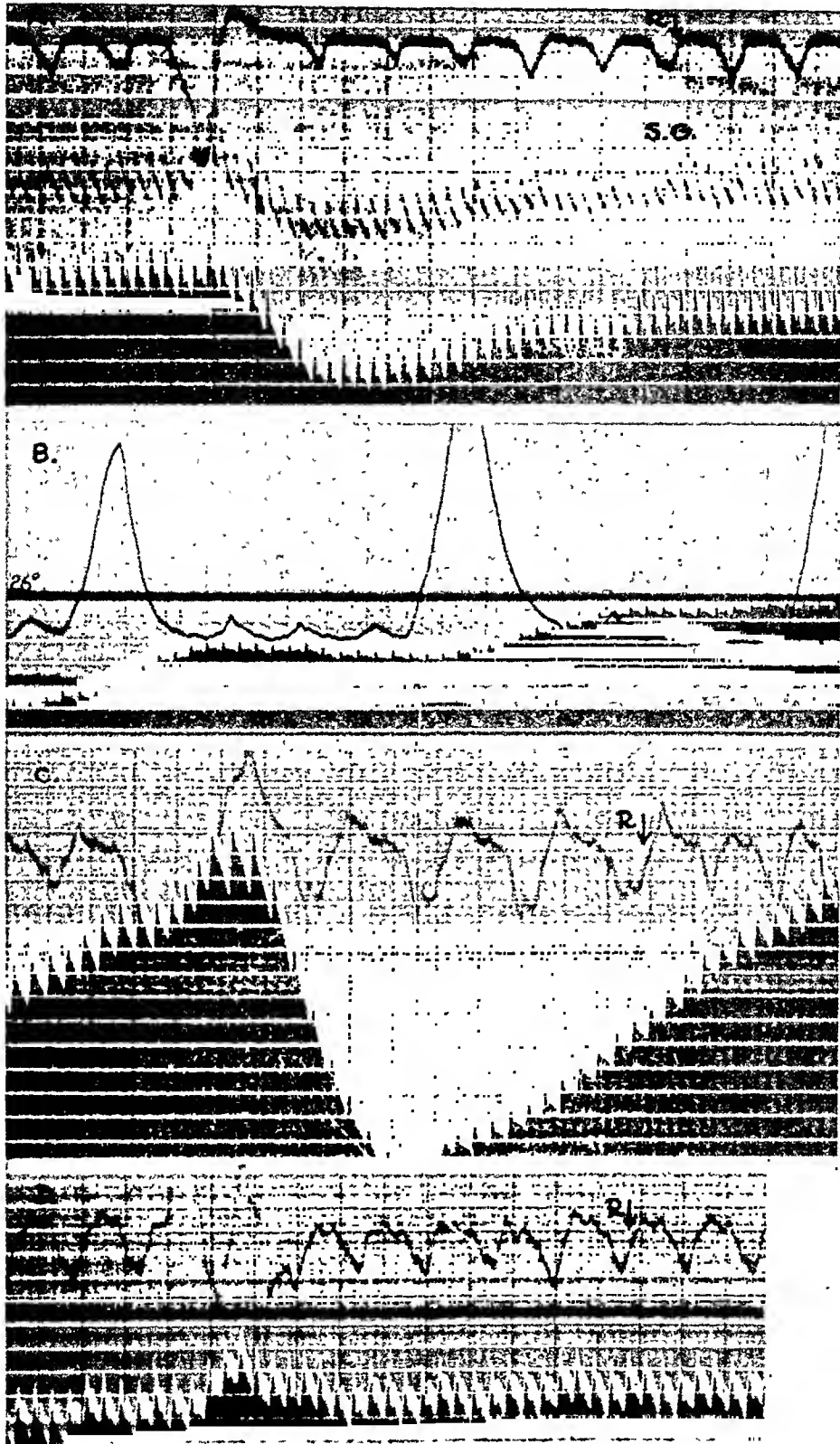


Fig. 6.—Effect of a deep inspiration upon blood flow through toe. *A*, Normal individual (first left toe) fully dilated. Skin temperature 32° C. *B*, Normal individual (first left toe) constricted. Skin temperature 26° C. *C*, Normal individual (first left toe elevated). Skin temperature 34° C. *D*, No response in sympathectomized extremity (nine years previously). Skin temperature 34° C. Reduction of original tracings to one-half. Room temperature 23° C. For abbreviations, etc., consult legend to Fig. 2.

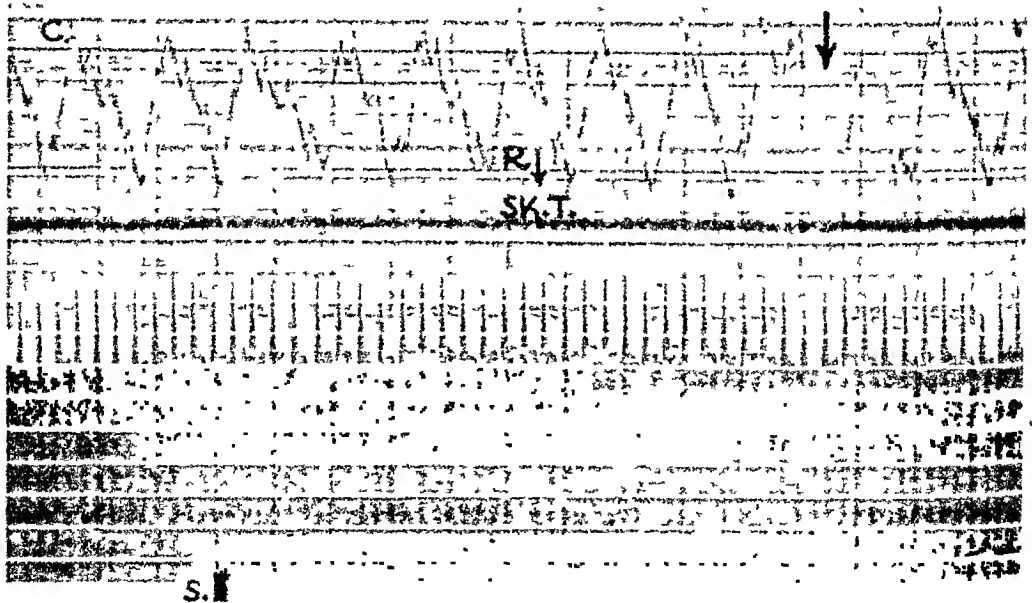
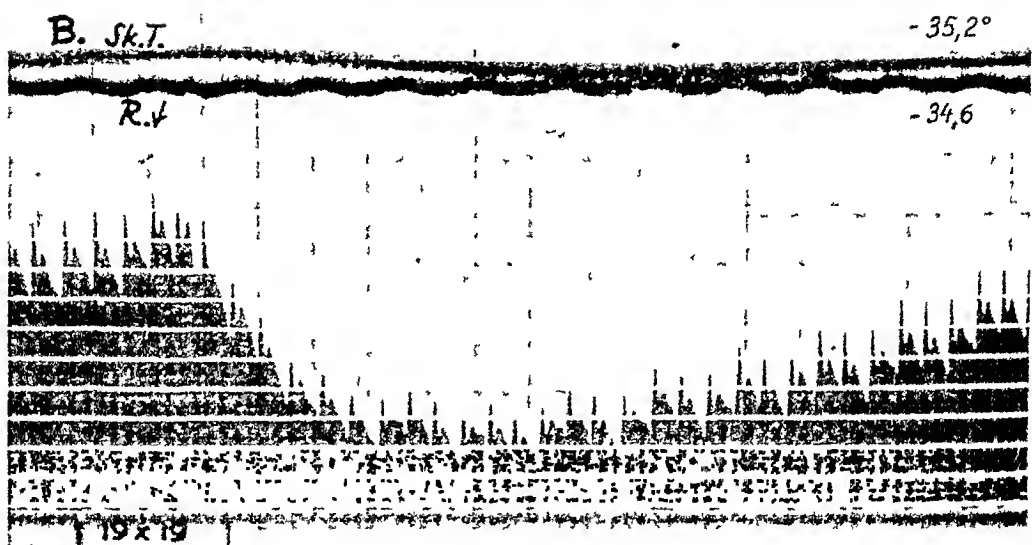
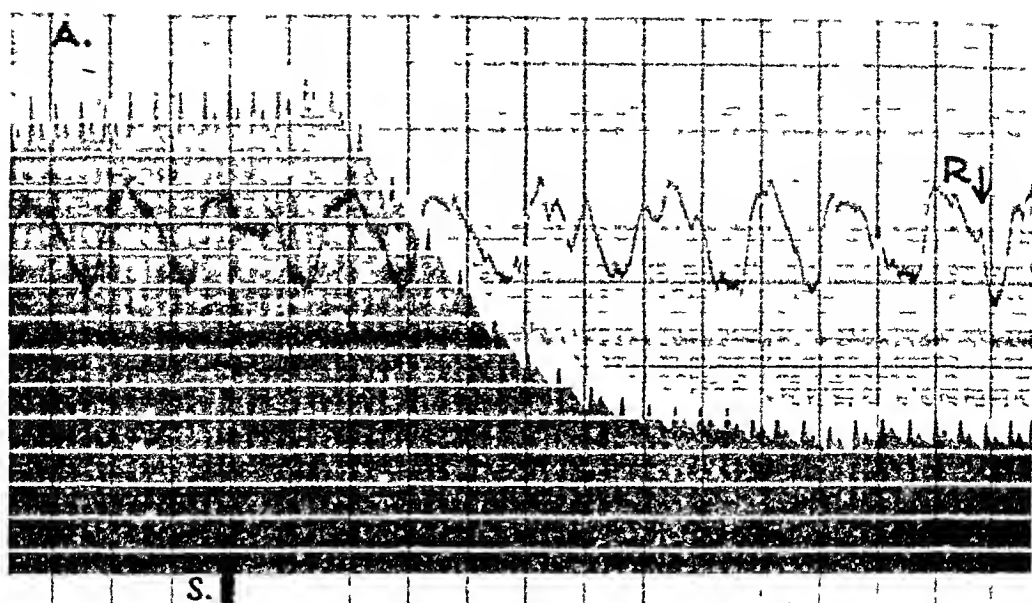


Fig. 7.—(For legend see opposite page.)

strictor reflex results from sudden inflation of a blood pressure cuff (Fig. 8, A). This may raise the systolic blood pressure by as much as 15 mm. of mercury. The clinical importance of such a reflex as regards the accuracy of blood pressure readings is worthy of further study. The diminution in digital volume from any of the constrictor reflexes just mentioned is greater in the elevated limb than in the dependent one for reasons mentioned previously, which suggests that the constriction is arterial rather than venous, in contrast to the opinion of some authors.^{2, 9}

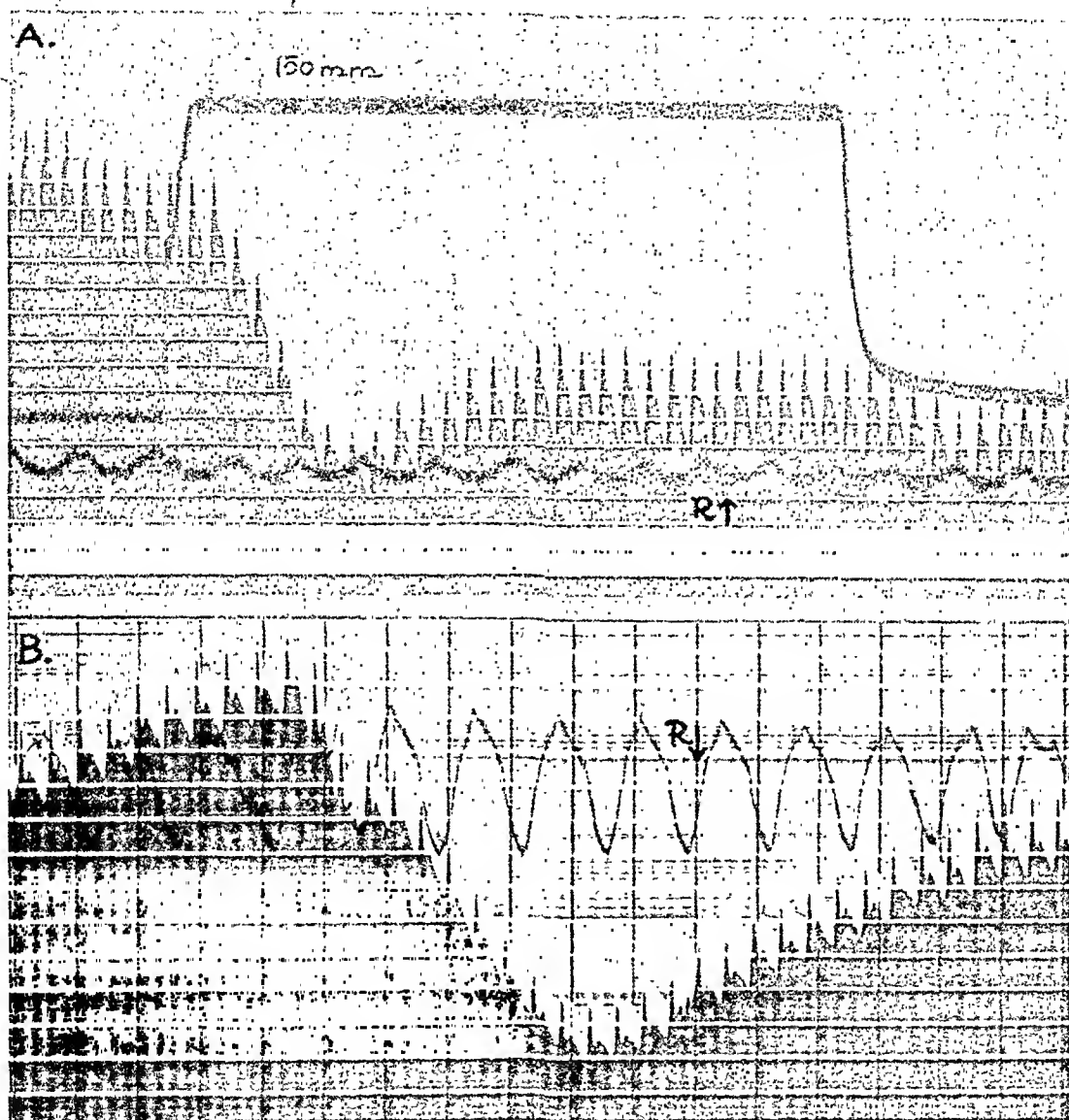


Fig. 8.—A, Effect of interruption of blood flow in an upper extremity upon blood flow through toe (first left toe). B, Fluctuations in blood flow occurring during venous congestion of 60 mm. Hg (first right toe). Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

Fig. 7.—Effect of unexpected noise (A) and mental strain (B) on blood flow through toe. Between the signals in (B) the subject was calculating the problem 19×19 . C, No effect in sympathetomized extremity (ten years previously). First left toe. At the arrow, accidental deep breath. Reduction of original tracings to two-thirds. Signal in A and C: unexpected noise. For abbreviations, etc., consult legend to Fig. 2.

B. The Rate of Blood Flow in the Toes.—*

1. Calculation of the Rate of Blood Flow: The venous congestion test previously described in detail²³ was employed to calculate the rate of blood flow in the toes. In brief, the rate of blood flow was determined by stopping the venous return from the toes by means of a blood pressure cuff fixed at the ankle, without impeding the arterial inflow. A normal tracing (Fig. 9, A) takes the following characteristic course: (a) it rises along a straight line, following this, (b) it slopes gradually until the vascular bed is filled, when (c) it runs parallel to the base line. When the pressure is released the tracing returns to the initial level, as a rule to within hundredths of a cubic centimeter. During the first part the volume increase per second is read; this serves as a measure of the arterial inflow. The rate of blood flow is then calculated per minute and for 100 c.c. of tissue from the following formula:

$$R = k \frac{I \times 100 \times 60}{V}$$

wherein: R = Rate of blood flow in cubic centimeters per minute.

k = Factor which is constant for a particular site of the cuff:
e.g., k = 3 if the cuff is fixed at the ankle (see second paragraph below).

I = Increase in digital volume per second in cubic centimeters.

V = Digital volume in cubic centimeters.

The results obtained with this method are very consistent and enable evaluation with great accuracy as long as the pressure of the cuff is well below the diastolic pressure. However, pressures below 30 mm. Hg are apt to give erroneous results.

The site of the congesting cuff is of importance for the correct calculation of the rate of blood flow. If two cuffs are fixed on the same leg, one being below the knee and the other at the ankle, the inflow tracing obtained in the latter case is steeper than that in the former. This difference in the gradient appears to be due to the difference in the amount of the venous network distal to the cuff. Therefore, for the correct measurement of the arterial inflow the cuff should be fixed at the base of the digit. In the case of the toes, however, this is impossible, and we have to apply the cuff at the ankle.

It had been found for the fingers²³ that the increase in volume per second from venous congestion applied at the basal phalanx was three times that obtained from congestion applied at the wrist. If we assume that the same relations exist in the foot, then we could assume that the increase in toe volume from venous congestion applied at the base of the toe would also be three times greater than that obtained from congestion applied at the ankle. Therefore the results obtained from congestion applied at the ankle have to be multiplied by three—the factor k in our formula—in order to obtain the actual rate of blood flow.

Following the release of the venous congestion the volume returns, as a rule, to the original level (Fig. 9, A). However, in some subjects a fall below

*The results refer to tests carried out with the patient in the reclining position.

the latter occurs, and it is immediately followed by a rise to the initial level (Fig. 9, *B*). Abramson and his coworkers,⁴ who also observed this phenomenon, took it for a reflex mechanism. Fig. 9, *B*, which was obtained in a patient with lumbar sympathectomy proves that, if this is a reflex, it cannot be a spinal sympathetic one.

2. Changes in the Rate of Blood Flow: The rate of blood flow fluctuates in accordance with changes in the height of the pulse volume which, as we have seen, in turn depends upon the vasomotor tone. The higher the pulse volume, the greater the gradient and the greater the rate of blood flow (Fig. 10). The rate of blood flow to the toes of normal subjects thus calculated varied between

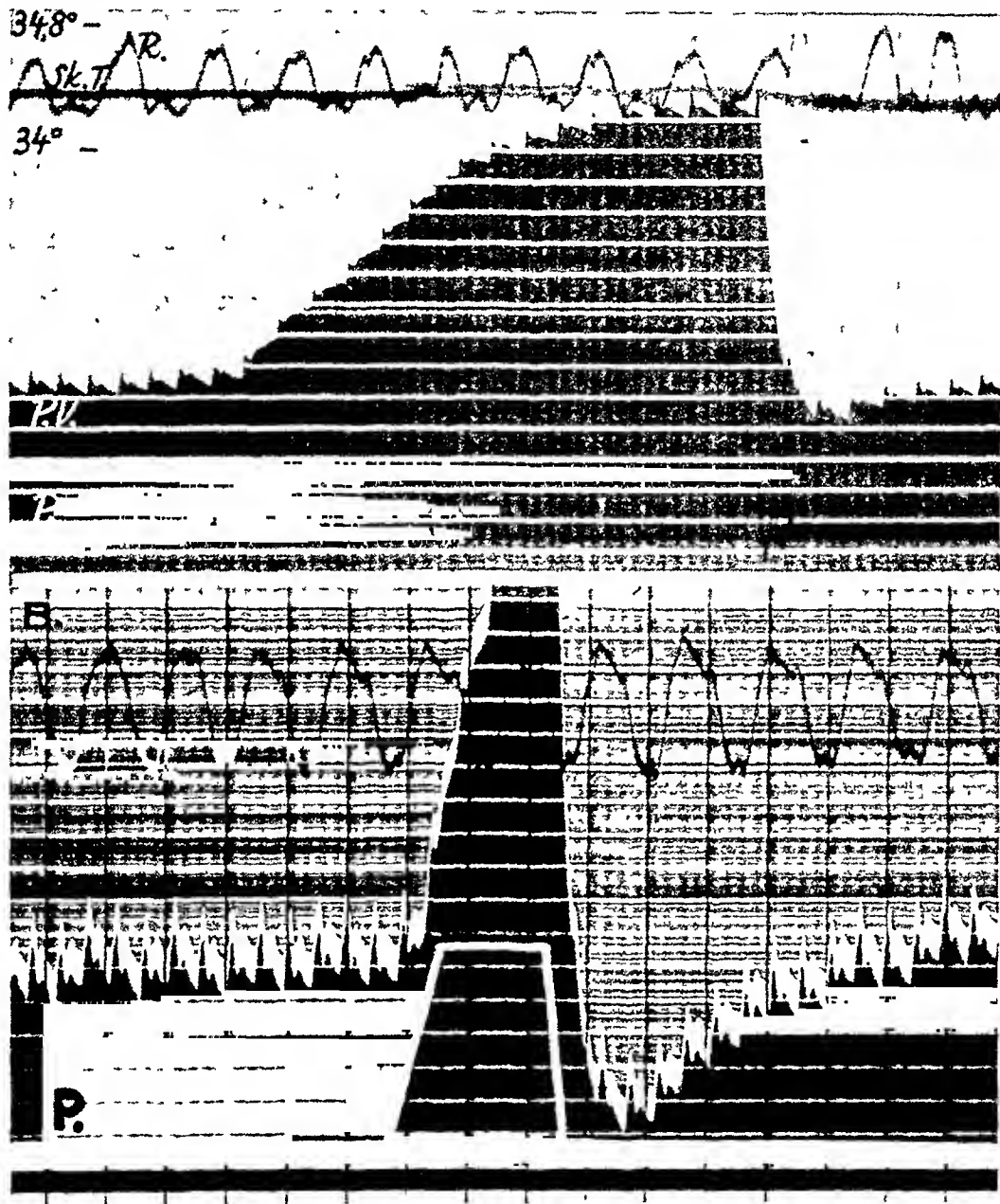


Fig. 9.—*A*, Typical tracing of venous congestion test (second left toe, fully dilated). Note initial rise along straight line and return to initial level with release of pressure. Skin temperature $\pm 34^{\circ}$ C. Room temperature 21° C. *B*, Venous congestion test (first right toe, sympathectomized) showing transient fall below base line with release of pressure. Skin temperature 34° C. Room temperature 23° C. Record of pressure has been retouched with white. Cuff applied at ankle in all tracings unless otherwise stated. Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

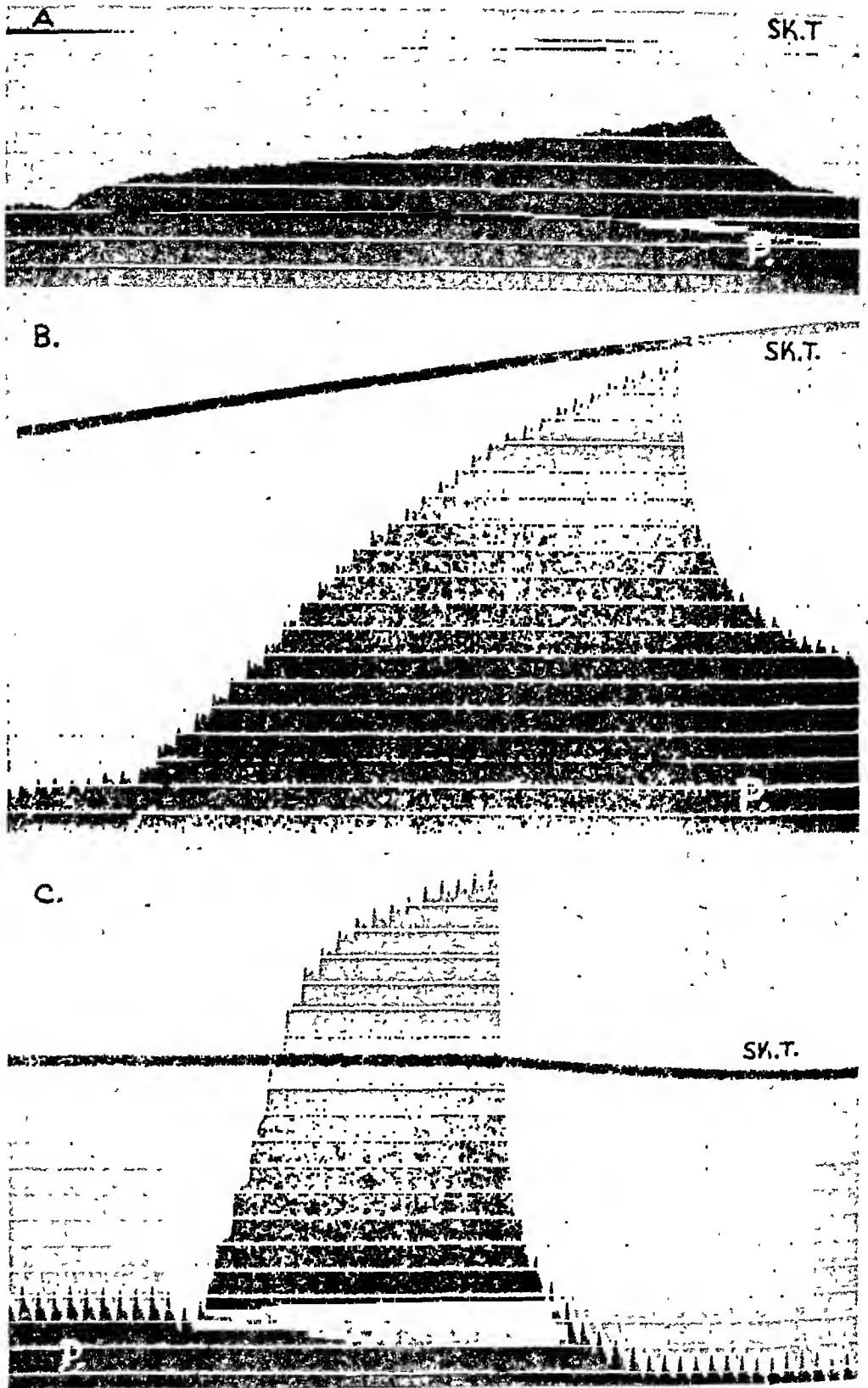


Fig. 10.—Effect of vasomotor tone on gradient of rise during the venous congestion test (first left toe). A. Full constriction; skin temperature 22°C . B. During dilatation, skin temperature $\pm 25^{\circ}\text{C}$. C. Almost fully dilated, skin temperature 24.9°C . Room temperature 21°C . Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

1 c.c. during full constriction and 90 c.c. per minute for 100 c.c. of tissue when fully dilated. These values compare very well with those obtained for the skin of the fingers, but are considerably higher than those calculated by Kunkel and Stead³⁰ for the foot.

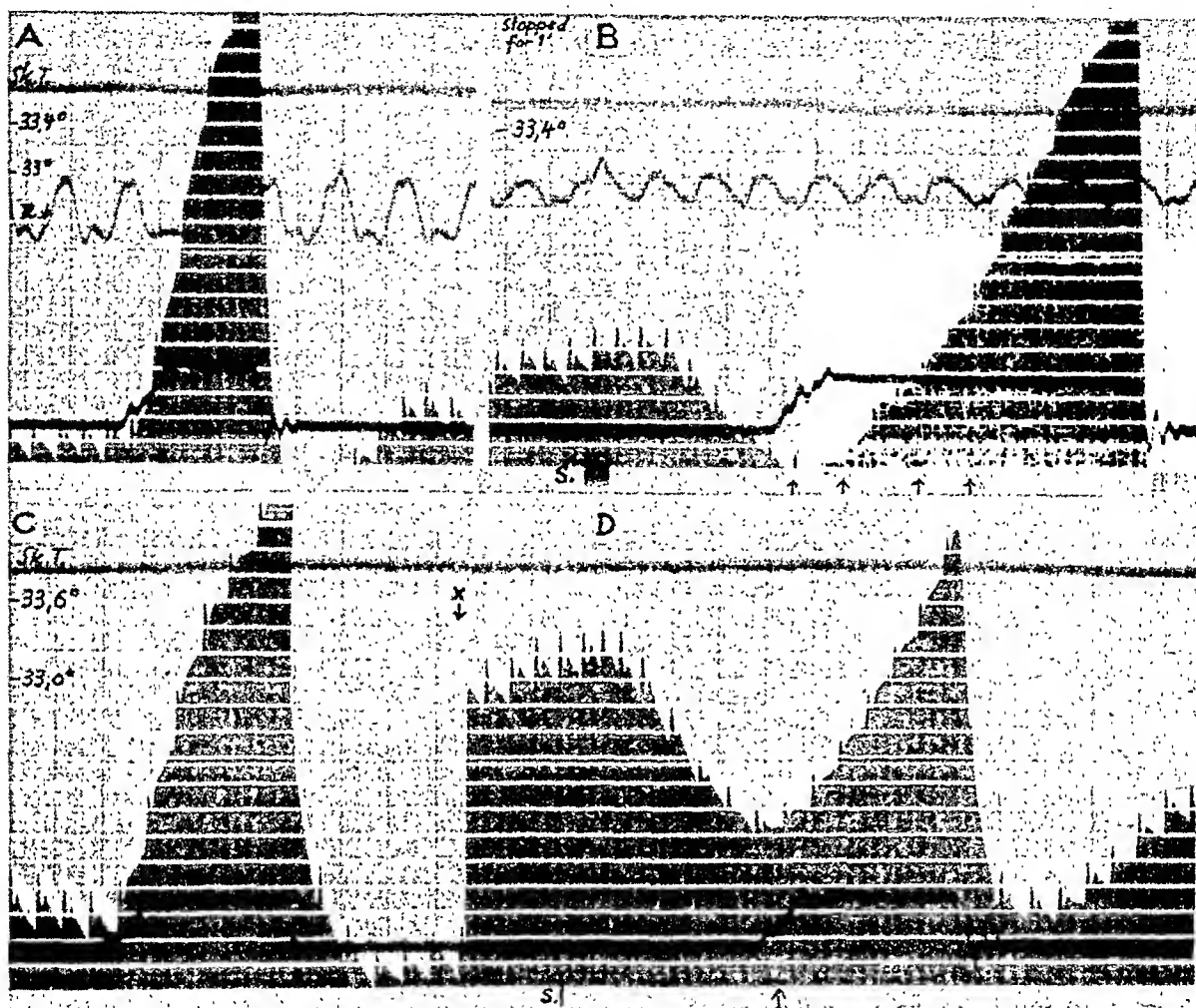


Fig. 11.—A and B, Effect of unexpected noise upon blood flow through toe (first left toe). Explanation in text. C and D, Effect of deep breath upon rate of blood flow through toe (first left toe). Cuff applied below knee. Explanation in text. Reduction of original tracings to two-thirds. At X adjustment of plethysmogram. For abbreviations, etc., consult legend to Fig. 2.

The changes in the rate of blood flow which result from reflex constriction, such as an unexpected noise or a deep breath, are illustrated by Fig. 11. In Fig. 11, A, venous congestion was applied during complete relaxation, the rate being 42 c.c. per minute for 100 c.c. of tissue. One minute later, at the signal (Fig. 11, B), an unexpected noise was made and peripheral constriction resulted. The pulse volume decreased from 0.022 to 0.01 cubic centimeter. Eight seconds later, at the height of the response, the venous return was arrested by the same pressure as was applied in Fig. 11, A. On account of the preceding vasoconstriction the increase in volume was less steep. In addition, the tracing is altogether differently shaped. It slopes upward. This is very similar in all tracings, and appears adequately to be explained by the wearing off of the constriction resulting in an increased arterial inflow with every consecutive heart-

beat. Thus the rate of blood flow calculated during the first two pulses is about 4.5 c.c. per minute, for the next three pulses it is 9 c.c., and it is 12 c.c. between the third and fourth arrows. From the fourth arrow onward, the rate of blood flow is 16.5 cubic centimeters.

Similarly, the constriction resulting from a deep inspiration can be analyzed (Fig. 11, *C* and *D*). Prior to the deep inspiration the blood flow was 50 c.c. per minute and for 100 c.c. of tissue (Fig. 11, *C*). At the height of the reflex constriction (Fig. 11, *D*) the rates of blood flow, starting at the arrow, were calculated as follows: 4 c.c., 12 c.c., 20 c.c., and, eventually, 30 c.c. per minute for 100 c.c. of tissue. When the pressure was released, the volume fell markedly below the initial level but rose immediately afterward. It was only then that the constriction wore off completely.

The effect of a chain of such constrictor impulses and the effect of smoking upon the peripheral blood flow have already been dealt with elsewhere.²²

C. The Effect of Body Heating.—Ever since the clinical importance of differentiating between arterial spasm and arterial occlusion was recognized, tests assessing the ability of the arteries to dilate have become an essential requirement in the study of peripheral vascular diseases. Of all the methods which have been recommended to relieve the vasoconstrictor tone, body heating has proved least objectionable and very satisfactory for clinical purposes. Gibbon and Landis¹⁸ produced reflex dilatation in the lower extremities by immersing both forearms in water to 42° to 45° C. They tried immersion of one hand as far as the wrist but this did not result in complete relaxation of the blood vessels of the feet. However, according to our experience, complete vasodilatation will readily result from immersion of *one* arm to a point about 5 to 7 inches above the elbow, provided the subject is covered with a woollen blanket to prevent the dissipation of heat.

Fig. 12 represents a typical response as obtained in a normal subject. When the rate of blood flow, pulse volume, digital volume, and skin temperature are recorded simultaneously it can be seen that pulse volume and digital volume are the first to rise after a small initial drop. It is only after the blood flow has been increasing for some time that the skin temperature starts rising. In our case both pulse volume and rate of blood flow reached their maximum dilatation level after twelve minutes. Digital volume and skin temperature, however, continued to rise for eight more minutes. The relation between the height of the pulse volume and the rate of blood flow, on the one hand, and the skin temperature on the other can be clearly appreciated, and it is obvious that the pulse volume furnishes the clearest picture of the state of the circulation at any one moment. In this person reflex dilatation occurred very rapidly since there was moderate dilatation at the outset. With vessels fully constricted there is, however, considerable delay, and dilatation often does not commence for eight to ten minutes.

In the opinion of Gibbon and Landis a normal response to body heating, that is, a rise in skin temperature to 32° C. or above within thirty to thirty-five minutes, "definitely excludes the possibility of obliterative structural disease of

the arteries as a cause of the diminished blood flow in the lower extremities.¹⁹³² This statement has been generally accepted, and skin temperature measurements have accordingly been evaluated for assessing the efficiency of the arterial circulation. However, on numerous occasions we have observed that the skin temperature reached the normal vasodilatation level (32° C.) within thirty minutes, yet the height of the pulse volume and the rate of blood flow remained

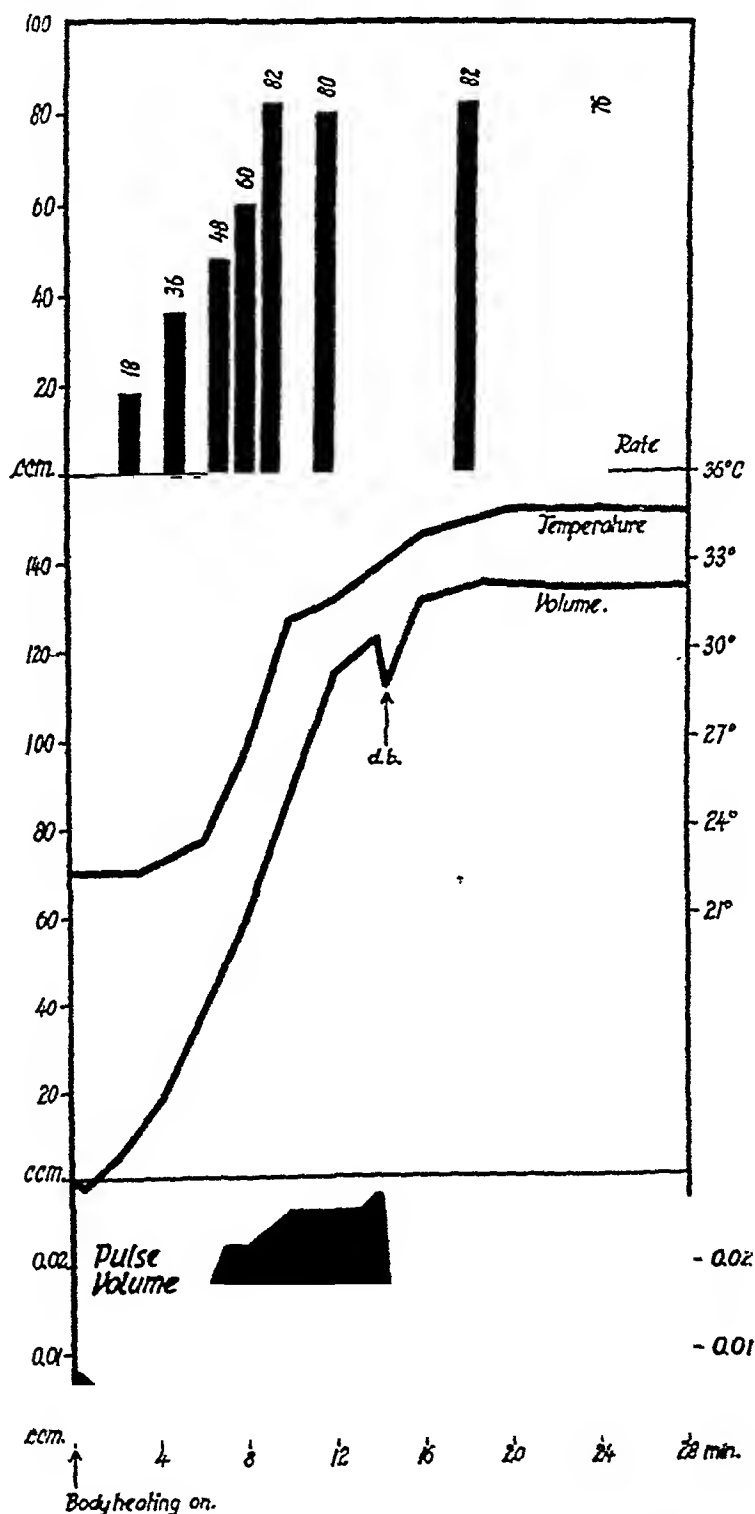


Fig. 12.—Effect of body heating upon the pulse volume, digital volume, skin temperature, and the rate of blood flow through the toe of a normal subject, all continuously recorded (first left toe). Room temperature 21° C.

considerably below the values seen normally during full vasodilatation (Fig. 13). Pulse volume and rate of blood flow therefore indicated organic vascular disease, whereas the skin temperature did not suggest this. Direct application of heat and paravertebral block did not furnish a higher pulse volume than did body heating. Fig. 14 shows the results of testing one of the arteries of the

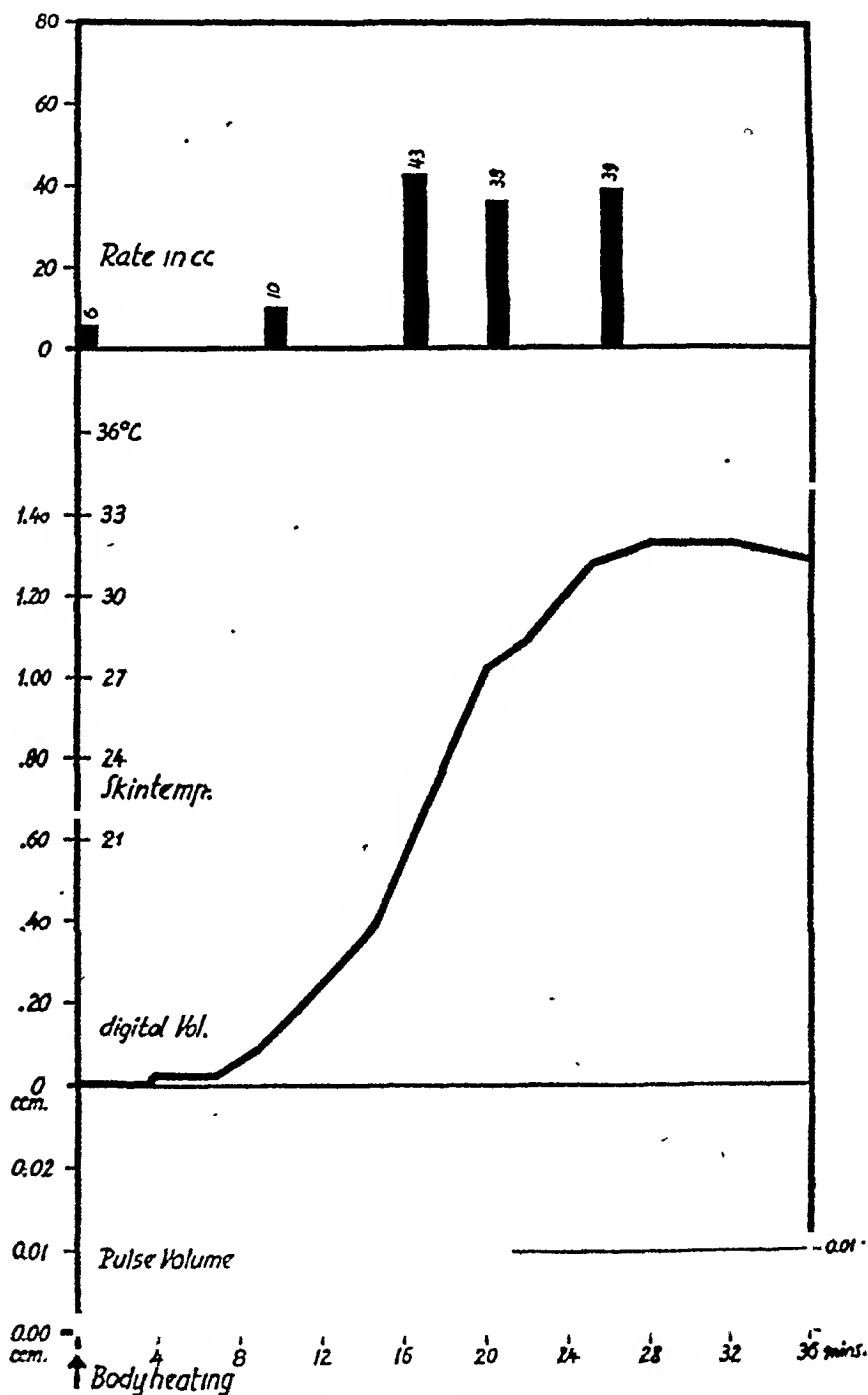


Fig. 13.—Effect of body heating upon pulse volume, digital volume, skin temperature, and rate of blood flow in a digit with moderate organic occlusion. Note normal response in skin temperature but decrease in pulse volume and rate of blood flow during full dilatation. Room temperature 21° C.

digit. There is no doubt that structural changes were responsible for the diminished pulse volume. These findings therefore illustrate two points: (1) a rise in skin temperature to the normal vasodilatation level in response to body heating does not exclude organic obstruction, and (2) digital plethysmography is capable of demonstrating structural changes in arteries at a stage when the skin temperature measurement is unable to detect them.

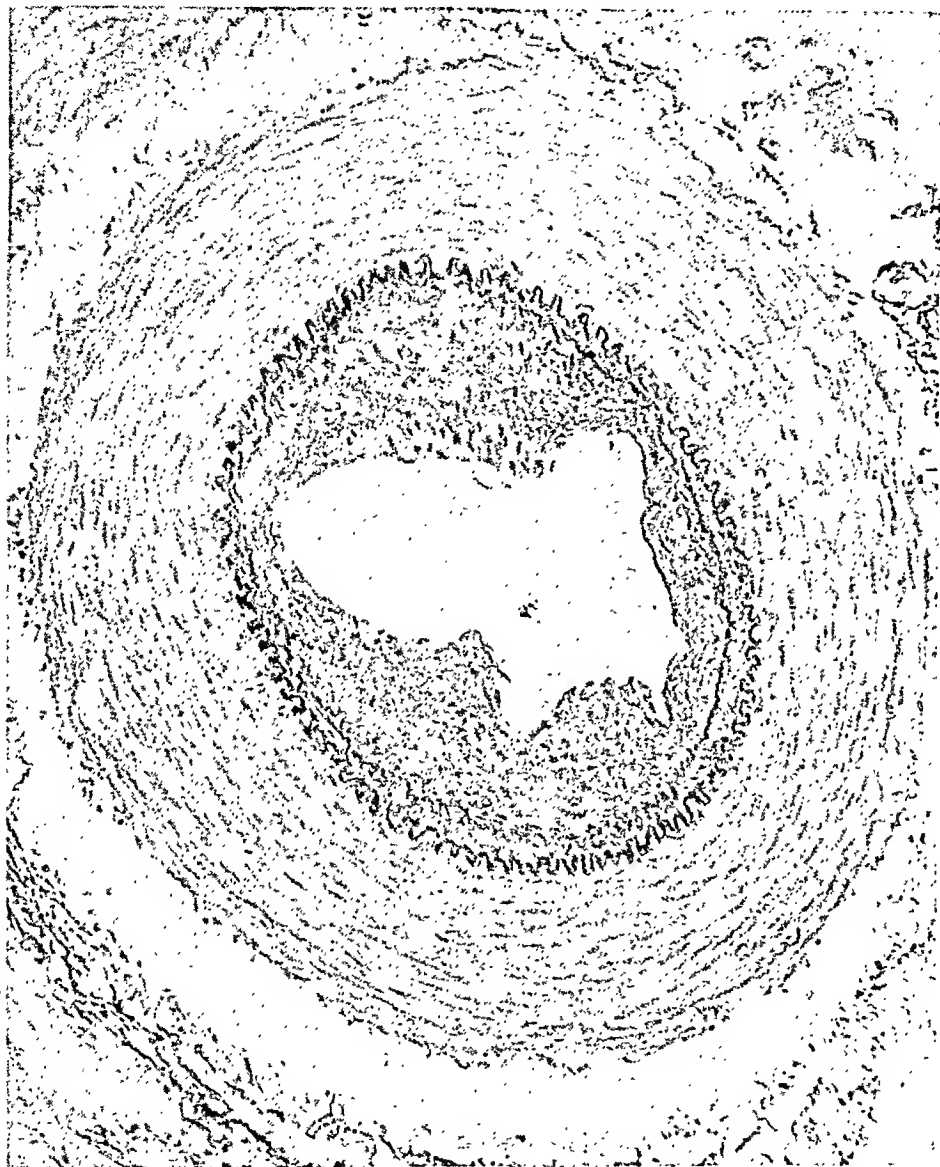


Fig. 14.—One of the arteries of digit examined in Fig. 13.

It has been generally accepted that vasodilatation induced in one extremity by warming another depends upon the return of warmed blood to the general circulation affecting the temperature-regulating center in the hypothalamus.¹⁷ However, Uprus, Gaylor, and Carmichael⁴⁴ pointed out that it is the gradient or steepness of the rise in blood temperature, rather than the actual temperature of the blood, which initiates reflex vasodilatation. We found that recognition of the latter fact is of great clinical importance because it constitutes a source of error in the immersion method hitherto not stressed. Obviously, in order to

obtain a sufficient gradient, the blood flow through the immersed extremity should be normal, otherwise little warmed blood will be returned. If the arteries of the immersed arm are partially or totally occluded, the blood will warm only very slowly and a slow gradient will result. Reflex dilatation may thus fail or be incomplete, and an organic occlusion may be simulated in an extremity where the blood flow is actually normal (Fig. 15). In such a case the diminished reflex dilatation is the result of organic occlusion of the vessels of the immersed extremity and not of the tested one, as can be proved by immersing another extremity whereupon a normal response is obtained (Fig. 15).

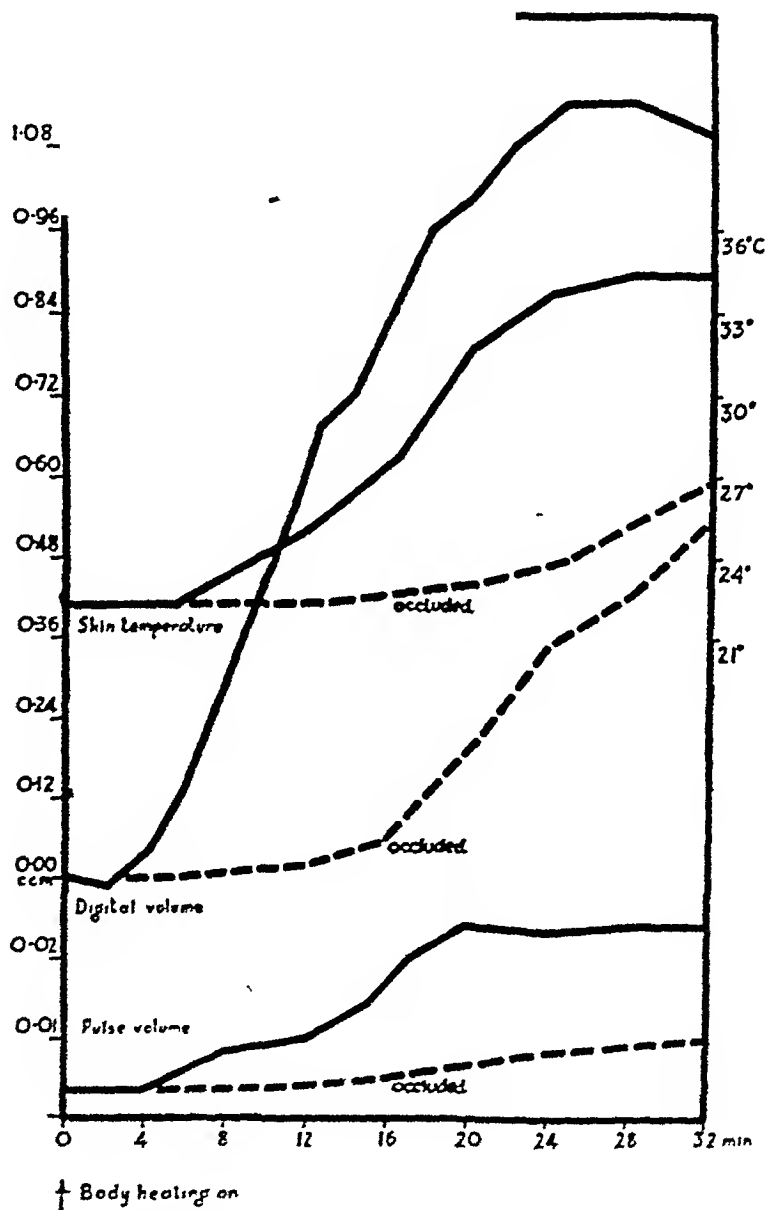


Fig. 15.—Effect of body heating resulting from immersion of an extremity with patent (black lines) and with markedly occluded arteries (interrupted lines) upon the blood flow through an extremity with normal arterial circulation. Room temperature 21° C.

Pickering and Hess³⁷ have already noted that body heating may not be an adequate procedure to dilate the vessels in the lower extremities of some normal subjects. In our series we had two subjects who were free from clinical signs of spastic vascular disease, such as Raynaud's phenomenon or acrocyanosis, but always had noticed that their extremities were cold and clammy.* Like

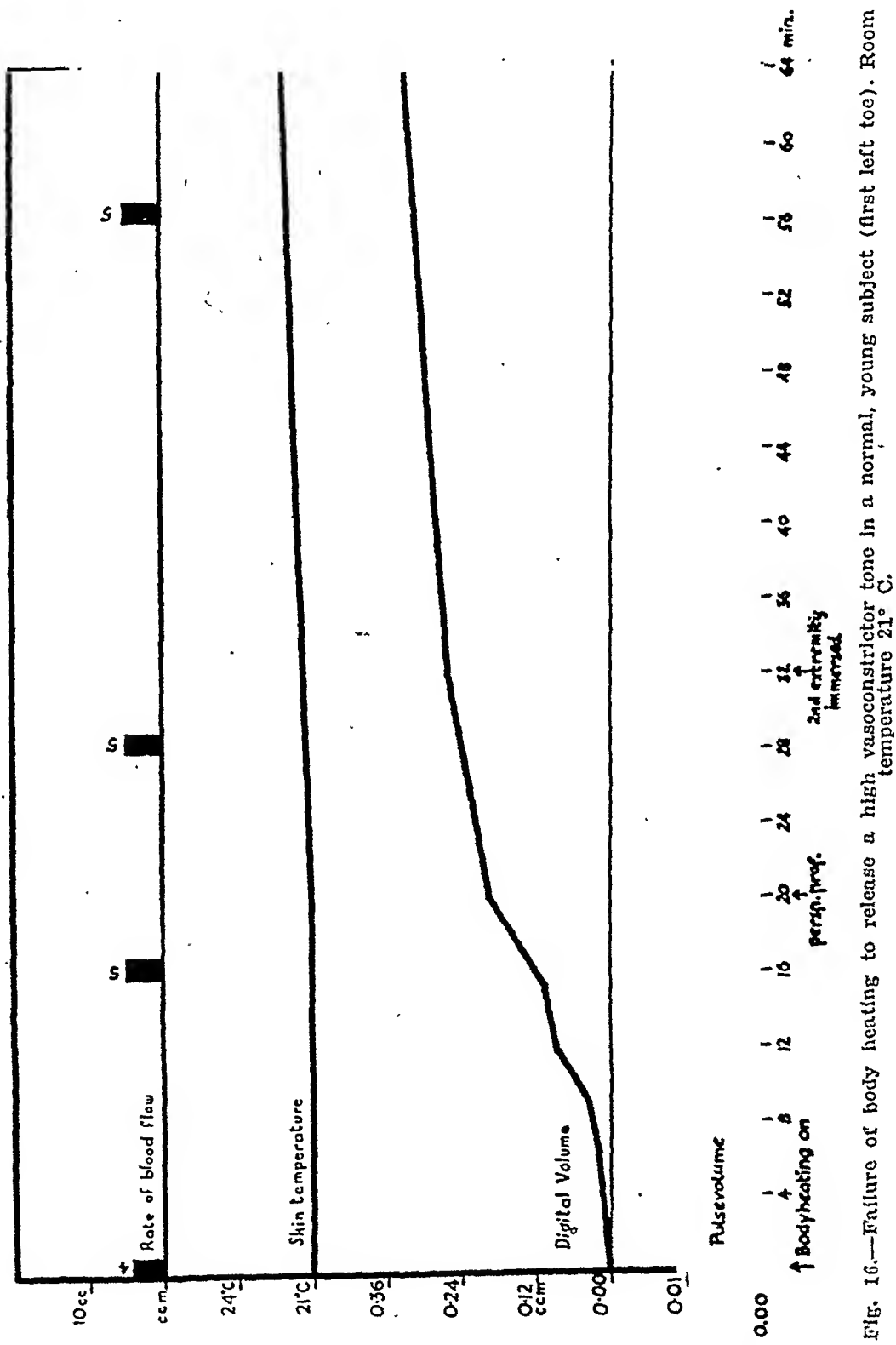


Fig. 16.—Failure of body heating to release a high vasoconstrictor tone in a normal, young subject (first left toe). Room temperature 21° C.

*It may be of significance that in one of them a suprarenal rest was found on operation for inguinal hernia.

all other persons they started to perspire profusely after twenty minutes' body heating, yet there was hardly any change in pulse volume, digital volume, or skin temperature within thirty minutes (Fig. 16). Immersion of an additional extremity for another thirty minutes did not produce the desired relaxation. Following the local application of heat, prompt relaxation of the vessels was obtained. The pulse volume rose to 0.025 c.e. (Fig. 17), and the rate of blood flow was 80 c.e., indicating that we were not dealing with an organic occlusion but a high vasomotor tone.

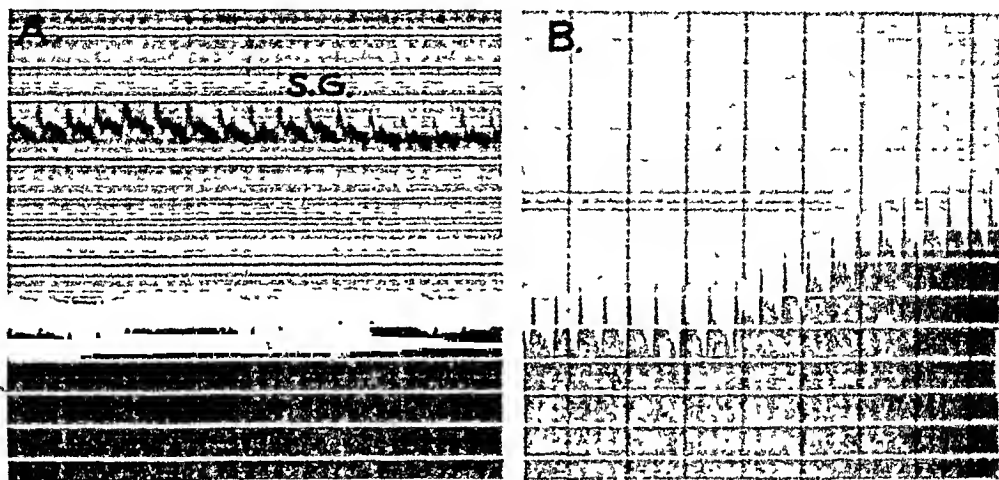


Fig. 17.—Pulse volume of a subject who did not dilate during body heating. A, After thirty-six minutes body heating (two extremities immersed). B, After foot had been immersed for ten minutes in water of 42° C. Room temperature 21° C. Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

D. The Blood Flow in Sympathectomized Extremities.—Following the interruption of the sympathetic pathways the spontaneous fluctuations in pulse volume and digital volume, as well as the constrictor reflexes following various intrinsic and extrinsic stimuli, are no longer obtained (Fig. 18). Body heating fails to produce reflex dilatation, indicating that the body is no longer capable of mobilizing the peripheral blood flow for body temperature regulation. Conversely, interruption of the sympathetic reflex arc may be diagnosed from failure to evoke these responses.

Following ganglionectomy, the tone of the peripheral vessels is mainly determined by three factors: (1) the local metabolic requirements of the tissues (effect of metabolites), (2) the local stimuli reaching the vessel wall directly from the outside, without the mediation of the nervous system (cold, etc.), and (3) the effect of endogenous substances (acetylcholine, epinephrine, etc.) reaching the vessel wall via the blood stream. Therefore, the blood flow of the

Fig. 18.—Pulse volume following lumbar ganglionectomy. Note absence of changes in height of pulse and digital volume. A, Sympathectomy for ulcers ten years previously. (At signals: pinpricks). First left toe. Skin temperature 33° C. At arrow, accidental deep breath. B, Sympathectomy for Raynaud's phenomenon eight years previously. First left toe. Skin temperature 32° C. Note organic involvement. C, Sympathectomy for early thromboangiitis obliterans nine years previously. First right toe. Skin temperature 24° C. D, Sympathectomy for early thromboangiitis obliterans nine years previously. First right toe, elevated. Skin temperature 30° C. At signal, unexpected noise. Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

SK.T.

S.

S.

B.

C.

D.

S.

Fig. 18.—(For legend see opposite page.)

sympathectomized extremity may not be the same when tested on different occasions. If such influences are depressing in nature, the blood flow tends to return to its maximum as soon as such stimuli are removed. For this reason, during rest under ordinary laboratory conditions, the blood flow through the sympathectomized lower extremity was found to be at its maximum.

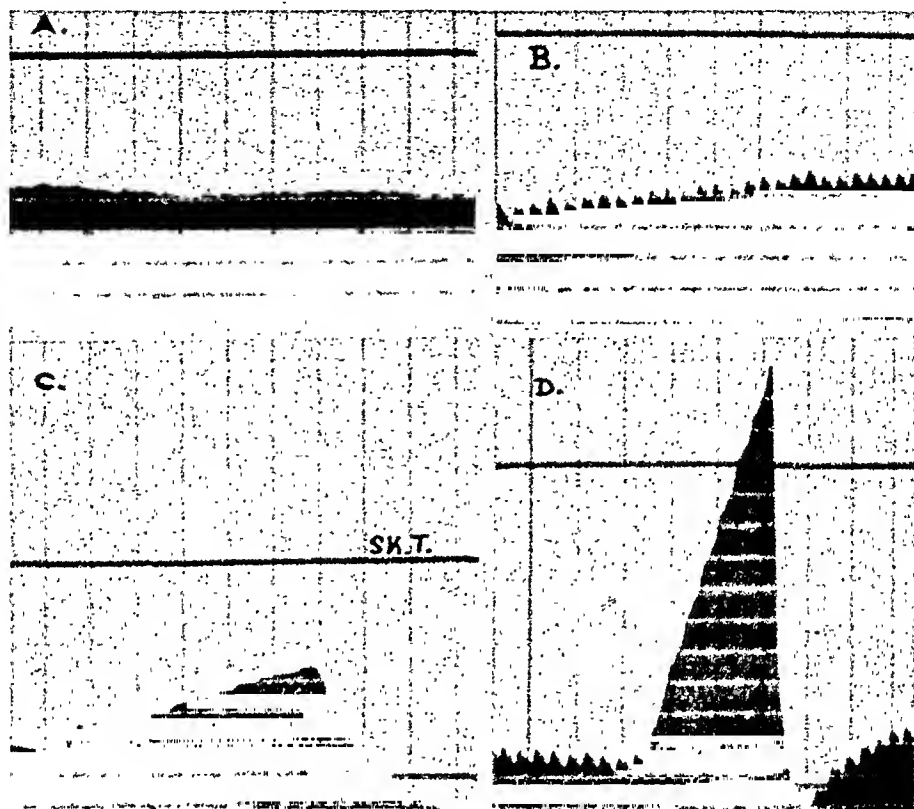


Fig. 19.—Subject with well-advanced thromboangitis obliterans with superimposed arterial spasm (first right toe). A, Pulse volume during rest. Skin temperature 24.5°C . B, Pulse volume fully dilated. Skin temperature 32.5°C . C, Venous congestion test during rest. D, Venous congestion test fully dilated. Room temperature 23°C . Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

As is generally accepted, following the degeneration of the autonomic (postganglionic) nerves after ganglionectomy, there occurs an increased sensitivity of the isolated structure to circulating epinephrine. This hypersensitivity which has been made responsible for the early return of the vasomotor tone in the upper extremities following the removal of the stellate ganglion^{15, 41, 47} does not enter the picture in this account, however, owing to the fact that ganglionectomy of the lower extremities does not remove the sympathetic ganglia supplying the sciatic nerve but interrupts their preganglionic fibers only. Degeneration of the sympathetic nerves to the foot therefore is not a feature of lumbar ganglionectomy and sensitization to epinephrine, which should theoretically be absent, is in fact minimal. Thus the aim of all ganglionectomies, namely permanent abolition of vasomotor tone, is more readily achieved in the lower

extremities. Thus we found in 29 patients in whom 51 lumbar ganglionectomies had been performed from one to eleven years previous to the last examination that the blood flow was still at its maximum and that there was no return of vasomotor tone as judged by the height of the pulse volume and the rate of the blood flow. There was no increase in blood flow following body heating. Obviously, even in the subject with sympathectomy of longest duration (Fig. 18, A) regeneration of the sympathetic fibers had not occurred, which bears emphasis in the light of the work of various authors.^{25, 43, 47}

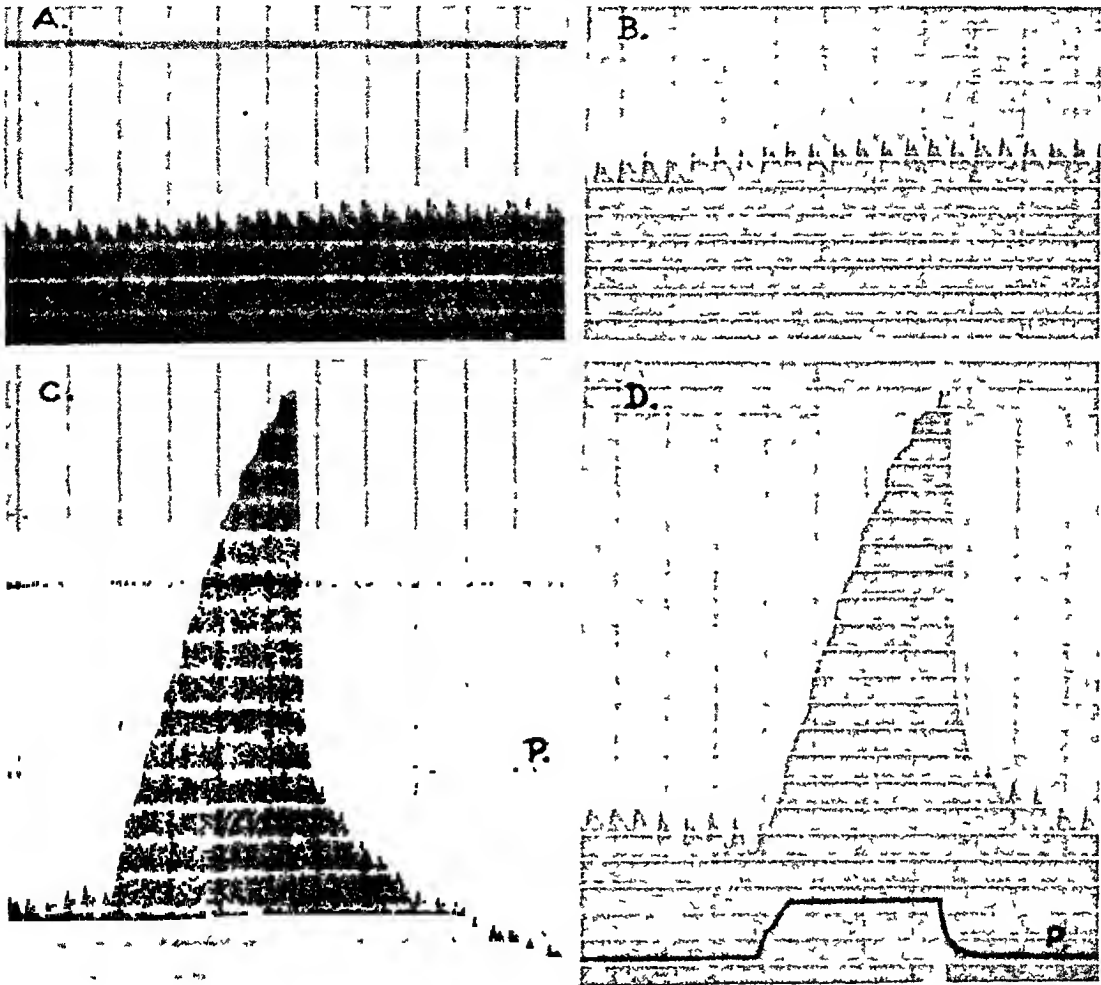


Fig. 20.—Same subject as Fig. 19 (first right toe). A, fourteen days after lumbar sympathectomy. Skin temperature 32° C. B, Thirteen months after sympathectomy. Skin temperature 34° C. C, Venous congestion (fourteen days after sympathectomy). D, Venous congestion (thirteen months after sympathectomy). Reduction of original tracings to two-thirds. Room temperature 22° C. For abbreviations, etc., consult legend to Fig. 2.

The indications for sympathectomy in peripheral vascular diseases depend upon the demonstration of a significant degree of vasoconstriction. The latter can be determined exactly by digital plethysmography and the amount of relaxation which can be expected to result from sympathectomy can be predicted exactly. Fig. 19 was obtained from a subject with histologically proved thromboangiitis obliterans, demonstrating the point in question. No pulse volume was registrable during ordinary laboratory conditions (Fig. 19, A), and the rate of blood flow amounted to 2.2 c.c. for 100 c.c. of tissue per minute (Fig. 19, C). Body heating, however, greatly increased the blood flow. The pulse volume rose

to 0.005 e.c. (Fig. 19, *B*), the skin temperature to 31° C., and the rate of blood flow increased exactly ten times to 22.5 e.c. (Fig. 19, *D*). Two weeks after the ganglionectomy the values for both pulse volume and rate of blood flow were at the preoperative vasodilatation level (Fig. 20, *A* and *C*) and when tested one year after the operation they had even increased slightly (Fig. 20, *B* and *D*).

In our cases where lumbar sympathectomies were performed for other than vascular diseases (e.g., ulcer cruris) both pulse volume and rate of blood flow reached and remained at the normal vasodilatation level (Fig. 18, *A*).

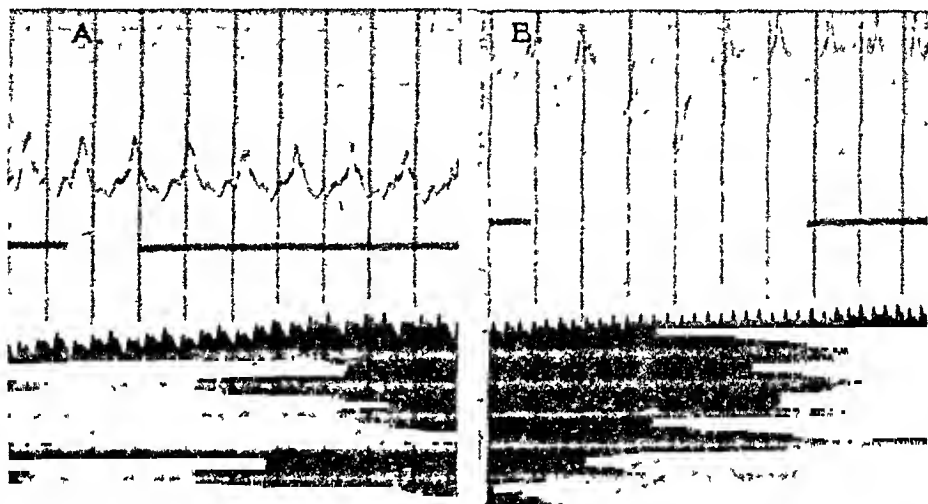


Fig. 21.—Decrease of pulse volume in sympathectomized extremity on body heating (same subject as Fig. 20, fourteen days after sympathectomy). *A*, Before body heating. *B*, After thirty minutes body heating. Reduction of original tracings to two-thirds.

In order to avoid confusion, all I have mentioned so far is that body heating does not increase the pulse volume and rate of blood flow in the completely sympathectomized extremity. The fact, however, is that both pulse volume and rate of blood flow decrease, often notably, with body heating (Fig. 21). The opposite may be observed following body cooling when pulse volume and rate of blood flow reach higher values. This decrease in blood flow following body heating has been explained as follows: At the outset it must be assumed that the blood is shunted away from the sympathectomized extremity. Then, since body heating causes a release of the vasomotor tone in the remaining normally innervated extremities, it follows that their vessels will offer less resistance to the blood flow as dilatation takes place, as contrasted with the vessels of the sympathectomized limb (the vascular tone of which remains uninfluenced by body heating and which consequently presents itself as being increased); and the blood flow, choosing the path of least resistance, will therefore be diverted from the sympathectomized extremity to the unsympathectomized one.

A similar phenomenon, occurring for the same reason, was observed in limbs showing marked signs of inflammation. Inflammation results in paralysis of vasoconstrictor tone, and body heating often does not raise skin temperature but decreases it in the inflamed limb.

These findings are not only of academic interest, but important in the management of peripheral vascular diseases in general and in sympathectomized limbs in particular. Methods normally known to cause increase in blood flow by reflex mechanisms may actually be contraindicated in the treatment of lesions in sympathectomized and inflamed extremities, since they may have the opposite of the desired effect.

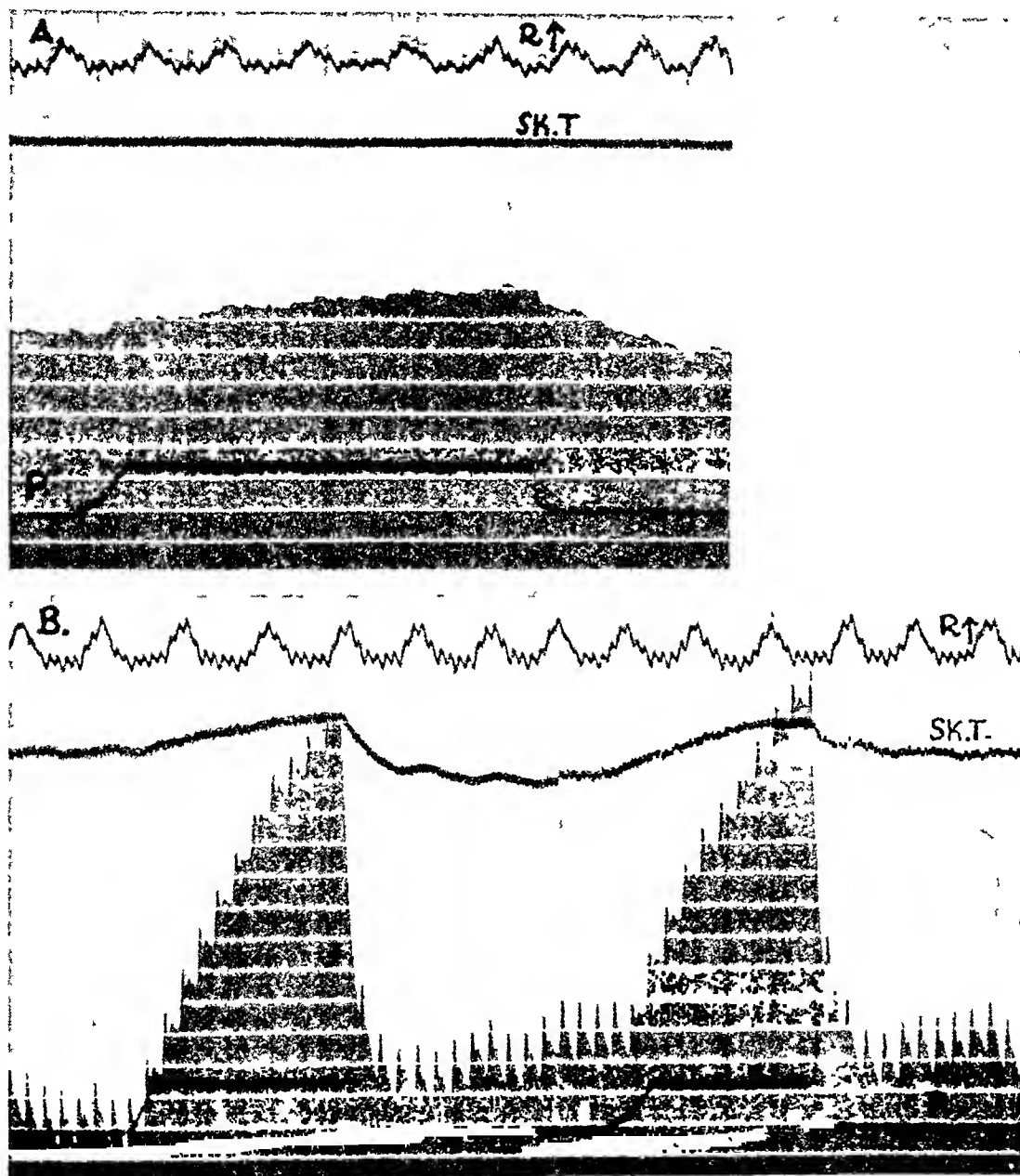


Fig. 22.—Case 1: Subject with Raynaud's phenomenon (first right toe). A, Venous congestion test during rest. Skin temperature 22°C . B, Venous congestion test during full dilatation. Skin temperature $\pm 34^{\circ}\text{C}$. Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

E. The Blood Flow in Peripheral Vascular Diseases.—It is outside the scope of this paper to deal with any of the vascular disorders in detail. We merely propose to demonstrate how our method may help in elucidating some of the more important clinical problems. Whenever a patient with symptoms

referable to the peripheral circulatory system is observed, three questions arise: (1) Is there an organic or a functional interference of the blood flow? (2) If organic, how advanced is the occlusion and to what extent are the vessels still capable of dilatation? (3) In cases where the main vessels are completely obliterated, how well has the collateral circulation been developed? It is true that skin temperature measurements will furnish some information, but it is the knowledge of the exact amount of blood flowing through the part which is so particularly helpful in organic occlusions, especially when it comes to the determination of the collateral circulation.

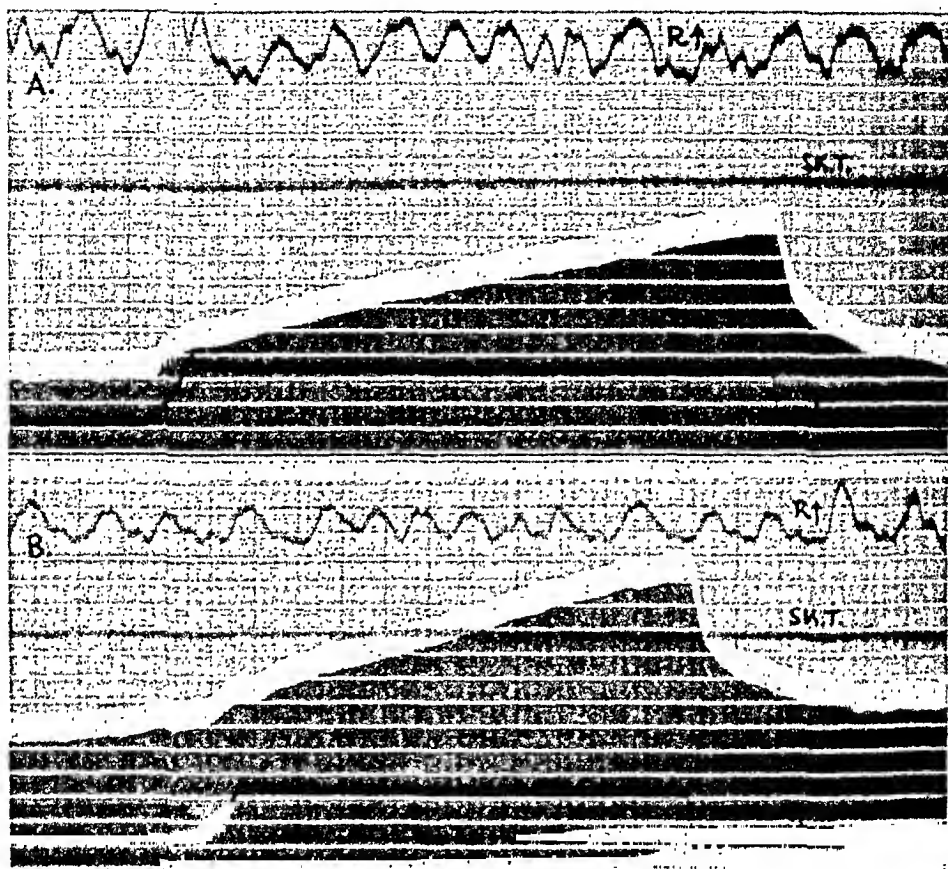


Fig. 23.—Case 2: Complete organic occlusion (first left toe). A, Venous congestion during rest. Skin temperature 28.7°C . B, Fully dilated. Skin temperature 29.3°C . Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

In Figs. 22, 23, and 24, three patients are presented, in all of whom there is a poor blood circulation during rest, as judged by the pulse volume and the rate of blood flow. However, in the first case, body heating results in a relatively normal response (Fig. 22). All values increase rapidly almost to within the normal limits. The diminished blood flow was therefore due to a high vasomotor tone only, there being hardly any organic interference demonstrable. The second case is exactly the opposite—no rise was noted either in pulse volume or in the venous congestion test with body heating (Fig. 23). The rate of blood flow remained almost the same. This is therefore a case of complete arterial occlusion. In the third case, as in the second, hardly any rise in pulse

volume was registered on body heating, which means that the main arteries must have been occluded. However, there was a marked increase in the rate of blood flow, which rose from 4.5 to 25 c.c. (Fig. 24). Obviously, it was the small collaterals in which the blood flow did not pulsate which dilated with body heating in this case. The venous congestion test, therefore, is capable of furnishing us with an exact measurement of the collateral circulation. A typical example of a case showing moderate organic occlusion associated with considerable spasm has already been demonstrated (Fig. 19).

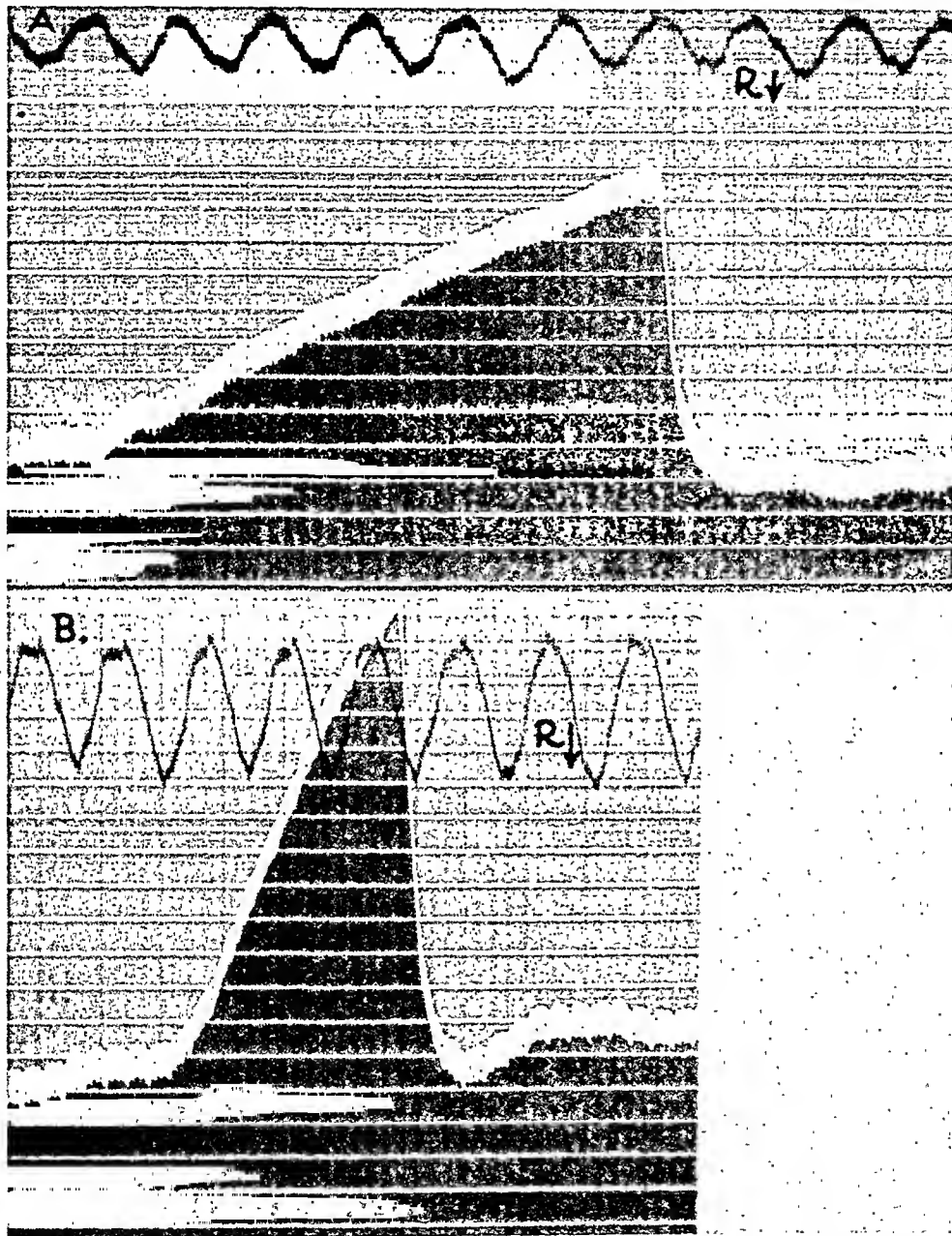


Fig. 24.—Case 3: Organic occlusion with well-developed collateral circulation (first left toe) (thromboangiitis obliterans). A, During rest. Skin temperature 22.5° C. B, Fully dilated. Skin temperature 28° C. Note the increase in venous congestion test out of proportion to minimal rise in pulse volume. Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

The degree to which the blood flow has to be diminished to cause death of tissue is surprising: reduction of the blood flow by 60 per cent has been found in many arteriosclerotic subjects who show no clinical manifestations of im-

paired peripheral circulation. This bears out the point made earlier that the blood flow through the digits serves other functions in addition to tissue metabolism. Permanent diminution of the blood flow to as little as 3 to 5 c.c. per minute for 100 c.c. of tissue occurred in some patients without causing gangrene.

According to these findings a rate of blood flow of 3 c.c. is all that is permanently needed for local tissue metabolism of the skin. This figure is somewhat higher than that computed by Burton.⁸ It is important to realize that in such cases gangrene may be precipitated not by deficient blood flow per se, but

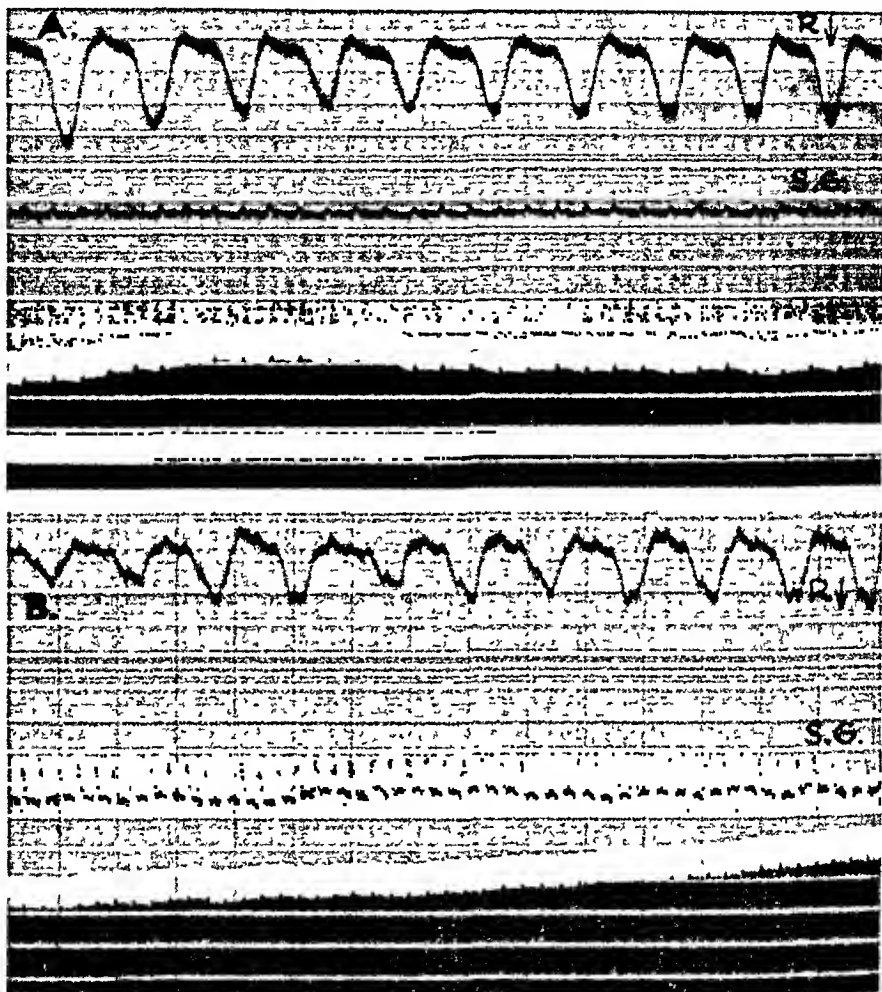


Fig. 25.—Plethysmogram and sphygmogram in two cases of diminished peripheral (ultimate) blood flow, but showing differences in penultimate circulation. A, first left toe. Skin temperature 19.5° C. B, first right toe. Skin temperature 21° C. Reduction of original tracings to two-thirds. For abbreviations, etc., consult legend to Fig. 2.

by a precipitating factor (such as heat and inflammation) suddenly demanding a higher amount of blood flow which in the organically occluded vessel is not forthcoming and which results in tissue death. It is not generally realized what degree of obstruction is required to produce a known reduction in blood flow. According to Poiseuille's law, the rate of blood flow changes as the fourth power of the radius of the vessel lumen. Diminution of the diameter of the lumen by one-half will therefore cause a drop in the rate of blood flow to one-sixteenth of that particular vessel.

Information as to the site of a peripheral obstruction of the blood flow may be obtained by recording simultaneously both the plethysmogram of a toe and the sphygmogram of the *arteria dorsalis pedis*. In both patients illustrated in Fig. 25 there was marked diminution of the peripheral blood flow, the pulse volume being only 0.002 cubic centimeter. In the first case, the excursions of the *arteria dorsalis pedis* were markedly diminished as well, demonstrating involvement of the whole arterial tree. Good excursions of the *dorsalis pedis* artery in the other case, however, placed the site of the interference at the arterioles, the penultimate circulation being hardly impaired.

DISCUSSION

Three values are furnished by the digital plethysmogram: (1) the pulse volume, (2) the digital volume, and (3) the rate of blood flow (by means of the venous congestion test). By recording simultaneously skin temperature and the excursions of one of the peripheral arteries a detailed analysis of the peripheral blood flow and vasomotor activity becomes possible. Of these, the height of the pulse volume is the most delicate indicator of both vasomotor activity and structural changes of the arteries. Its normal range varied between 0.002 c.c. during full constriction and 0.045 c.c. with full dilatation. The lowest value recorded during full dilatation in normal subjects was 0.02 c.c. and is referred to as the minimum vasodilatation level. These values compare very well with the height of the pulse volume previously recorded in the fingers.^{20, 21, 23} Failure of the pulse volume to reach the minimum vasodilatation level has yet to be accounted for.

While the pulse volume is intimately correlated with the actual rate of blood flow, and can therefore be used as an index for detailed analysis of the latter, the arterial inflow can be measured exactly by the venous congestion test. Its range varied between 1 c.c. per minute for 100 c.c. of tissue during full constriction and 90 c.c. per minute during full dilatation. The latter value is about four times higher than that calculated by Kunkel and Stead³⁰ for the whole foot, while the lower range is about the same, suggesting that it constitutes the minimal requirement for tissue metabolism. In the upper extremities similar relations exist, the blood flow through the hand being about one-fourth of that through the fingers.²³

The possibility exists that such a wide range in blood flow under the control of the autonomic nervous system is part of the body's mechanism for temperature regulation. The skin acts, as Sheard puts it, as an enormous dam with many gateways placed across the stream of internal heat, which can be opened and closed as occasion demands. Indeed, Winslow, Herrington, and Gagge⁴⁹ found that, by adjustment of the peripheral circulation, the effective thermal conductivity of the tissue may be modified over a fivefold to sixfold range. It is by means of the sympathetic tone that the blood flow through the extremities is set to the level prescribed by the demands of thermoregulation. Consequently, the tone of the vessels of the fingers under ordinary circumstances (room temperature, 20° to 23° C.) is about midway between full dilatation and full constriction, allowing the necessary adjustment.²³ In the toes, however, the vaso-

motor tone is, as a rule, considerably higher; and the blood flow, being near the lower limit, is not mobilized for thermoregulation. However, the picture changes and the vasomotor tone of the toe vessels decreases to take part in thermoregulation the moment the capacity of the blood flow through the fingers has been fully utilized. Dissipation of heat is initiated by the hands and forearms and continued by the feet and legs. These findings agree well with the observations of Roth, Horton, and Sheard³⁹ that the skin temperature of the toes noticeably exceeds room temperature only when that of the fingers fluctuates between 33° and 35° C.

Once the high vasomotor tone of the toe vessels has been overcome, spontaneous changes in the blood flow through the toes occur just as they were recorded in the fingers. They are best studied with the limb elevated when changes both in pulse volume and in toe volume assume very marked proportions. They are less prominent when the limbs are dependent. Abramson and Katzenstein² reported that spontaneous fluctuations are characteristic for the hands but that they are absent or insignificant in the feet. Our investigations make it more than likely that the reason for his apparent difference between the upper and lower extremities is due to differences in posture and is not the result of differences in vasomotor activity. In Abramson and Katzenstein's tests the foot was obviously dependent.* There can be no doubt that spontaneous changes in blood flow are typical for both fingers and toes—they can be readily recorded under identical conditions which includes identical vasomotor tone and identical hemostatic conditions. Since they are more prominent in the elevated extremity we conclude that they are arterial rather than venous in origin, in contrast to the view of Abramson.

Ever since Brown-Sequard⁷ called attention to the clinical importance of differentiating arterial spasm from arterial occlusion, tests measuring the degree of both have become an essential requirement in the study of peripheral vascular diseases. Of these the immersion test introduced by Gibbon and Landis^{18, 21} has proved a very efficient and unobjectionable method of producing reflex dilatation. Pickering and Hess,³⁷ however, in one apparently healthy subject, failed to obtain relaxation of the vasomotor tone of the feet with immersion of the hands and concluded that warming of the body removes only part of the constrictor tone of the feet, "the remainder being more or less permanent unless the sympathetic fibres are blocked." The studies in our series did not corroborate this. Whenever body heating released vasomotor tone complete dilatation was produced. The height of the pulse volume and rate of blood flow obtained after body heating corresponded well with the values obtained following direct application of heat or during paravertebral block.

Body heating is a most effective method of producing complete reflex dilatation. However, similarly to the case already reported by Pickering and Hess, in two of our own cases body heating failed to release vasomotor tone. Therefore, in subjects who do not respond to body heating, but in whom there is obviously incomplete organic occlusions on clinical examination, we produce

*No mention of the position is made.

maximal dilatation by following body heating with the local application of heat. The question of whether we are dealing with an organic or a functional state is then easily answered. This simple method can be used with great advantage in conjunction with plethysmography, but it is obviously useless if the circulation is assessed by means of skin temperature measurements and when more complicated methods like paravertebral block or spinal anesthesia have to be resorted to to assure release of vasomotor tone.

Gibbon and Landis^{18, 32} have already recognized that it is the increase in blood temperature due to the return of heated blood from the immersed extremity acting upon the thermosensitive centers in the hypothalamus which initiates general reflex vasodilatation. Pickering³⁶ estimated that a rise of 0.01° to 0.04° C. is sufficient to produce this effect. Soon afterward Carmichael and his coworkers⁴⁴ pointed out that it is the gradient or steepness of the rise rather than the actual temperature of the blood itself which initiates relaxation. Thus, the rate of blood flow through the immersed extremity becomes an important factor in securing vasodilatation. With organic occlusion of the arteries in the immersed extremity, the amount of heated blood returned will be insufficient to produce the necessary gradient and dilatation may be incomplete or absent, even if the vessels of the tested extremity are absolutely normal. This is not a theoretical possibility but occurs in practice. Indeed, in the disorders seen in the majority of patients, such as thromboangiitis obliterans and arteriosclerosis, involvement of all extremities to varying degrees is the rule. Thus, failure of the immersion method to produce reflex dilatation may not mean necessarily organic occlusion of the limb tested, but may mean organic occlusion of the immersed extremity, nothing being revealed about the vessels in the extremity under examination. Obviously, this source of error is not inherent in methods producing dilatation by interrupting the sympathetic pathways or by direct application of heat.

Gibbon and Landis^{18, 32} were of the opinion that a rise in skin temperature to 32° C. within thirty to thirty-five minutes "definitely excludes the possibility of obliterative structural disease of the arteries," a view which now is generally held. Accordingly, Jahsman and Durham,²⁷ discussing the early recognition of arterial disease, state that "such a response excludes the possibility of obliterating structural disease of the arteries." Our investigations do not support their statements. Indeed, the blood flow measured plethysmographically may be diminished by as much as 60 per cent before significant alterations in the response of the skin temperature to body warming occur! A normal skin temperature after body heating, then, is no criterion as to the efficiency of the arterial circulation. The skin temperature response to body heating is not impaired in early organic involvement of the arteries, whereas the pulse volume in plethysmographic tracings is already markedly decreased. Realization of this fact becomes of paramount importance today when one is called upon to examine apparently healthy young men of our Armed Forces for what appear to be minor complaints but in whom the question of vascular disease arises. By waiting for the skin temperature to indicate arterial deficiency all the early cases of disease will be missed and in many of them a good prognosis vitiated.

Plethysmographic investigations therefore become almost essential since it may not be possible without them to answer the question of early structural changes.

The following sentence from Freeman and his co-workers' recent article¹ represents the typical opinion prevailing today as to the significance of skin temperature readings: "With a cool room temperature (20° C.) a rise in skin temperature to 31° C. means that the flow of blood is equal to that of a normal person with full vasodilatation. This level is reached in a limb with no arterial occlusion or with arterial occlusion which has been completely compensated for by collateral circulation." This statement admits that skin temperature readings do not indicate whether there is a normal blood flow or an arterial occlusion which has been compensated for by the development of a collateral circulation. The distinction between the two, one being normal, the other an indication of a serious pathologic event, is of considerable importance for the individual concerned and can by no means always be decided on clinical evidence. Neither does the fact that the arterial occlusion has been compensated for by a collateral circulation indicate that the underlying disorder has been arrested. By assessing the degree of both arterial occlusion and collateral circulation in such a case, plethysmographic investigations will assist us greatly in arriving at the correct diagnosis and prognosis.

Kramer²⁹ in his monograph on peripheral vascular diseases states that the usefulness of the plethysmograph is "more along the lines of investigation work and physiological research." I hope to have made it clear that the method developed by me lends itself at least as well to routine clinical examinations and furnishes information which cannot be obtained by any other method. The time has arrived when its wider use in clinics can be advocated. Its essentiality in recognizing early structural changes has been stressed. In differentiating occlusive from spastic vascular disease it has the advantage of supplying exact figures for the rate of blood flow, permitting exact estimation of the relative degree of each in a mixed case. In advanced cases the evaluation of the peripheral circulation revolves round the presence or absence of an adequate collateral circulation which can readily be determined by the venous congestion test. Such information is of prime importance because the principles on which the treatment of these groups must rest differ radically.

SUMMARY AND CONCLUSIONS

A plethysmographic method for measurement of the blood flow through the skin of the toes is described. The method is sensitive enough to register the blood flow through even a small toe in all its detail. The plethysmogram obtained furnishes three values: the pulse volume, changes in the digital volume, and, by means of the venous congestion test, the rate of blood flow. Of these, the height of the pulse volume was found to be an exquisite indicator of both organic occlusion and vasomotor tone. It varied normally between 0.002 c.c. during constriction and 0.045 c.c. during full dilatation.

Under ordinary laboratory conditions the vasomotor tone in the lower extremities is much higher than that of the upper ones, their blood flow not being mobilized for body temperature regulation like that of the hands. Dissipation

of heat is primarily effected by the hands and forearms, and only when their capacity has been fully exhausted does the vasomotor tone in the toe vessels decrease and then their blood flow is used for body temperature regulation. Data furnished suggest that this mechanism is the result of man's assumption of the upright posture. Spontaneous changes in blood flow are less prominent in the lower extremities on account of the high vasomotor tone, but they become equally marked, as in the upper extremities, once identical conditions prevail.

The rate of blood flow varied normally between 1 c.c. during full constriction and 90 c.c. per minute for 100 c.c. of tissue during full dilatation.

The effect of body heating as obtained by immersion of an independent extremity was studied. It is the gradient of the rise in blood temperature effect by the heated blood returned which initiates dilatation. Thus, a normal blood flow through the *immersed* extremity becomes very important.

It was found that the blood flow need not be normal if the skin temperature reaches 32° within thirty minutes (the "normal vasodilatation level") but may be markedly diminished as judged by the results of plethysmographic investigations. Plethysmography is therefore essential for detecting early structural lesions. The histologic appearance in such a case is shown, proving the point in question.

Once the release of the vasomotor tone is initiated, dilatation is maximal with body heating. However, two cases are cited in which release of vasomotor tone did not occur with body heating. Local application of heat in these cases easily demonstrated the patency of the vessels.

The indication for sympathectomy is discussed. In our cases following lumbar sympathectomy there was no return of vasomotor tone in the toes, and no regeneration could be demonstrated. In the sympathectomized extremity body heating decreases the pulse volume, by diverting blood from the sympathectomized extremity to the normal ones. Its clinical importance was stressed.

It is shown that the study of peripheral vascular disease is greatly assisted by plethysmographic investigations. Exact information becomes available as to the degree of occlusion, the degree of spasm, and the degree of the collateral circulation. By recording simultaneously excursions of one of the palpable arteries, the skin temperature, and the plethysmogram, detailed analysis of the peripheral blood flow becomes possible.

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ELECTROCARDIOGRAPHIC CHANGES IN CASES OF INFECTIOUS HEPATITIS

STUDY OF ELEVEN CASES OCCURRING IN AN EPIDEMIC

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THE sinus bradycardia observed in cases of jaundice is well known, but we have been unable to find any report of clinical electrocardiographic observations in the literature. Several experimental studies in animals have been made in order to determine the mechanism of the bradycardia and of the lowering of the blood pressure. A recent epidemic of infectious jaundice gave us an opportunity to study the electrocardiograms of this disease; eleven cases were studied during the height of the jaundice and after recovery.

REPORT OF CASES IN EPIDEMIC

In all, there were twenty-four cases of infectious hepatitis. The patients were all medical students and were in normal physical condition previously.

In none of the subjects had there been vaccination for yellow fever or other inoculation immediately preceding the outbreak. All the patients were members of one fraternity and ate at the same table. The subjects were all febrile, the temperature in some cases rising to 40° C. and above. All patients survived, and there were no sequelae. Other than the bradycardia, there were no cardiac symptoms. The Wassermann and microprecipitation tests were negative in all instances. The cephalin flocculation test was positive in all cases. The agglutination test for *Leptospira icterohaemorrhagiae* was negative in all cases. The clinical data are summarized in Table I.

TABLE I. CLINICAL FEATURES

CASE	TEMPERATURE (°C.)		BLOOD PRES- SURE	LEUCOCYTES (PER CU. MM.)		ALBUMIN IN URINE	ICTERUS INDEX		LIVER*
	ADMIS- SION	HIGHEST		ADMIS- SION	HIGHEST		ADMIS- SION	HIGHEST	
1	38.6	38.6	120/80	5,400	8,600	0	7	15	+ T
2	37.6	38.0	120/70	5,750	6,750	tr	24	24	+ T
3	39.6	39.6	120/70	5,600	8,200	tr	20	20	+ T
4	40.2	40.2	130/80	2,700	5,650	0	6	55	+ T
5	40.1	40.1	145/70	5,850	8,550	0	11	26	+ T
6	39.3	39.9	130/60	5,800	8,800	S.P.T.	16	24	T
7	37.2	37.9	120/75	5,950	6,100	0	14	19	+ T
8	37.9	38.4	120/80	6,350	9,050	S.T.		35	T
9	38.4	39.3	130/80	5,050	6,000	0	7	11	+ T
10	39.6	40.5	100/60	5,200	5,700	S.P.T.	17	22	+
11	37.5	37.5	Not re- corded	5,200	5,200	0	45	45	+ T

*+, palpable; T, tenderness; tr, trace; S.P.T., slightest possible trace.

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TABLE II. COMPARISON OF T-WAVE CHANGES WITH DEGREE OF JAUNDICE

CASE	HEART RATE PER MINUTE		T WAVE (HEIGHT IN MM.)			ICTERUS INDEX
	ILLNESS	RECOVERY	ILLNESS	RECOVERY	RECOVERY	
1	70	73	Lead I	2.0	3.5	15
			Lead II	3.0	5.5	
			Lead III	1.5	1.5	
2	68	84	Lead I	2.5	3.5	24
			Lead II	2.5	4.5	
			Lead III	1.0	1.5	
3	61	93	Lead I	1.75	2.5	20
			Lead II	3.5	4.0	
			Lead III	1.5	2.0	
4	66	63	Lead I	2.5	3.5	55
			Lead II	2.0	3.5	
			Lead III	-1.0	+-	
5	66	100	Lead I	2.0	2.0	26
			Lead II	2.5	3.0	
			Lead III	1.0	1.0	
6	52	91	Lead I	0.75	1.5	24
			Lead II	0.5	1.0	
			Lead III	+-	+-	
7	56	73	Lead I	1.75	2.5	19
			Lead II	0.5	1.0	
			Lead III	-1.0	-1.0	
8	80	75	Lead I	2.0	4.0	35
			Lead II	2.5	5.5	
			Lead III	1.0	1.5	
9	55	76	Lead I	3.0	4.0	11
			Lead II	5.0	4.0	
			Lead III	1.5	1.0	
10	102	48	Lead I	1.5	2.5	22
			Lead II	2.5	4.0	
			Lead III	1.5	1.5	
11	64	59	Lead I	2.0	2.0	45
			Lead II	1.5	2.0	
			Lead III	-0.5	1.0	

ELECTROCARDIOGRAPHIC FINDINGS

Electrocardiograms were taken in all eleven cases (Leads I, II, and III) on admission and after recovery. Table II is a summary of the heart rate, the height of the T wave, and the icterus index.

On comparing the T-wave changes with the icterus index, no correlation was seen. Likewise the temperature had little influence on the heart rate—some of the higher rates were found in the patients with lower temperatures and with high icterus indices, as noted in Table I.

In all instances, normal mechanism was present and, with it, sinus arrhythmia. In eight of the cases there was a moderate bradycardia during the height of the disease, and in two cases the heart rate was slightly higher than after convalescence. In one instance there was no change in heart rate.

TABLE III. Q-T INTERVAL DURING JAUNDICE AND AFTER RECOVERY

CASE	HEART RATE		CYCLE LENGTH		K ($Q-T = K \sqrt{C}$)	
	JAUNDICED	RECOVERY	JAUNDICED	RECOVERY	JAUNDICED	RECOVERY
1	70	65	0.86	0.92	0.389	0.376
2	68	75	0.88	0.80	0.384	0.369
3	61	67	0.98	0.90	0.390	0.40
4	66	80	0.91	0.75	0.379	0.392
5	66	72	0.91	0.83	0.379	0.362
6	52	69	1.15	0.87	0.391	0.375
7	56	68	1.07	0.88	0.396	0.395
8	80	84	0.75	0.71	0.393	0.392
9	55	65	1.09	0.92	0.383	0.385
10	102	65	0.59	0.92	0.391	0.376
11	64	75	0.94	0.80	0.392	0.381

TABLE IV. EFFECT OF EXERCISE

CASE	AT REST		AFTER EXERCISE (HOPS)	
	HEART RATE	T WAVES (MV)	HEART RATE	T WAVES (MV)
1	65	Lead I 0.35	86	Lead I 0.25
		Lead II 0.50		Lead II 0.35
		Lead III 0.10		Lead III 0.10
2	75	Lead I 0.35	96	Lead I 0.35
		Lead II 0.45		Lead II 0.40
		Lead III 0.15		Lead III 0.10
3	67	Lead I 0.20	82	Lead I 0.15
		Lead II 0.35		Lead II 0.30
		Lead III 0.15		Lead III 0.10
4	80	Lead I 0.30	113	Lead I 0.15
		Lead II 0.25		Lead II 0.15
		Lead III -0.10		Lead III -0.10
5	72	Lead I 0.20	84	Lead I 0.15
		Lead II 0.30		Lead II 0.25
		Lead III 0.10		Lead III 0.10
6	69	Lead I 0.10	84	Lead I 0.10
		Lead II 0.10		Lead II 0.10
		Lead III -0.05		Lead III -0.05
7	68	Lead I 0.25	88	Lead I 0.15
		Lead II 0.10		Lead II 0.15
		Lead III -0.10		Lead III -0.05
8	84	Lead I 0.40	103	Lead I 0.25
		Lead II 0.55		Lead II 0.40
		Lead III 0.15		Lead III 0.15
9	65	Lead I 0.40	78	Lead I 0.40
		Lead II 0.40		Lead II 0.45
		Lead III 0.10		Lead III 0.15
10	65	Lead I 0.25	107	Lead I 0.15
		Lead II 0.40		Lead II 0.30
		Lead III 0.15		Lead III 0.20
11	78	Lead I 0.20	88	Lead I 0.15
		Lead II 0.20		Lead II 0.20
		Lead III 0.10		Lead III 0.05

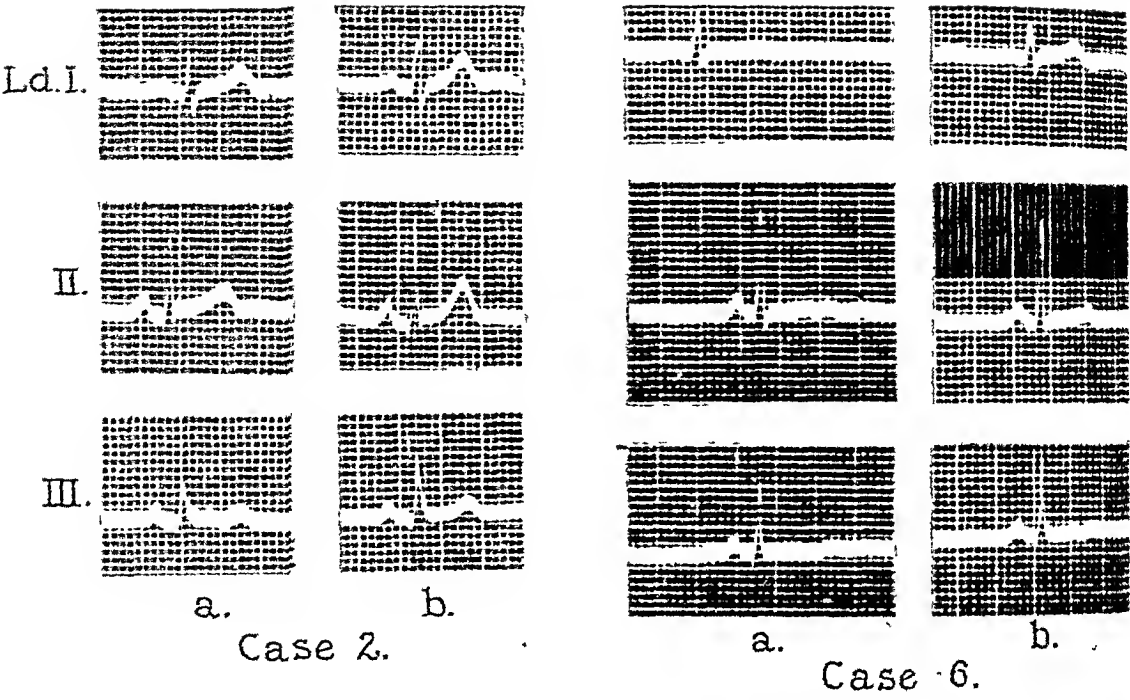


Fig. 1.

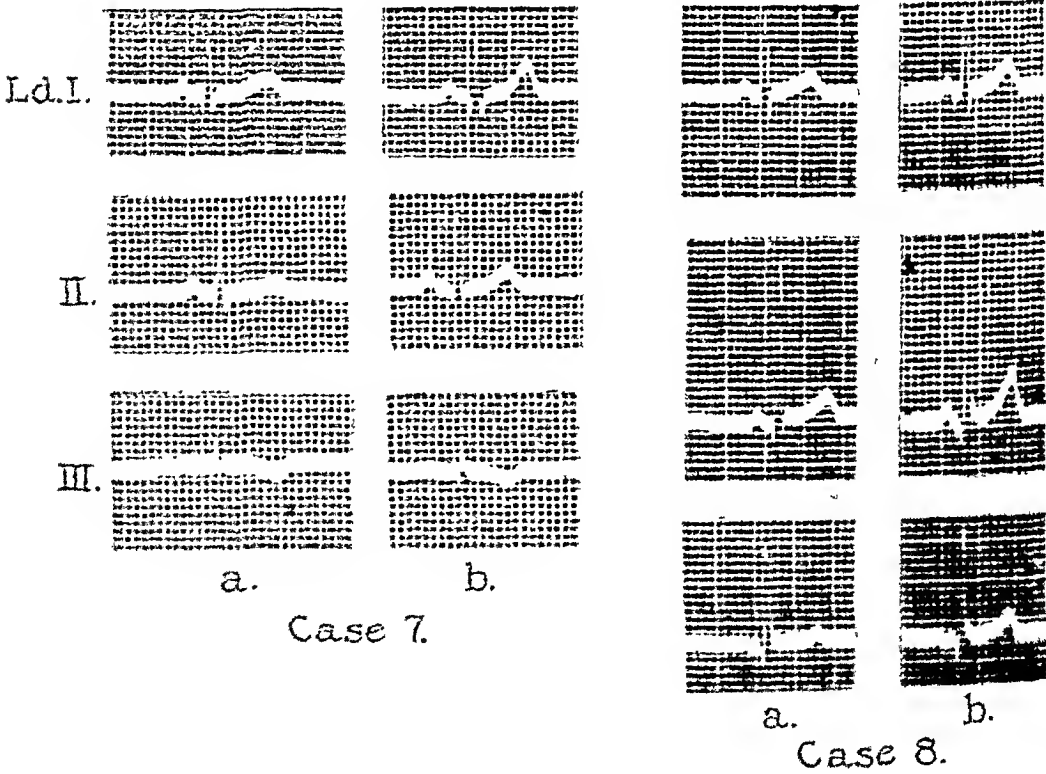


FIG. 2.

P-R Interval.—This, in all cases but one, was normal and was unchanged after recovery. In one case the P-R interval was 0.2 second during the disease and 0.16 second after recovery.

The QRS Complex.—There was a decrease in the voltage of the QRS complex in some of the cases. The QRS interval was unaltered.

Q-T Interval.—This was compared with the calculated value for the corresponding heart rate ($Q-T = K \sqrt{VC}$). K was within normal limits during the disease and was unaltered after recovery (Table III). The normal value of K for males is 0.397 with a range of between 0.337 and 0.433.¹

P Wave.—The P wave was normal in all cases except in Case 3, in which P_3 was inverted during the period of jaundice; it became upright after convalescence. In this case, the P wave was inverted again after exercise.

R-T Segment.—There was no change in the R-T portion of the curve.

T Wave.—In nine out of eleven records, the T wave was lower during the period of jaundice. This flattening of the T deflection was noted especially in Leads I and II. After convalescence was completed the T waves became normal and, in six cases, resembled records taken two years previously. In Figs. 1 and 2 are the electrocardiograms of four of the cases (a) during the height of the disease and (b) after recovery.

MECHANISM OF ACTION OF JAUNDICE ON THE HEART

Several possible factors in producing the electrocardiographic changes may be suggested. Bunting and Brown² reported finding, in the myocardium, hyalinization and necrosis of the cells, to which they attributed the death of their rabbits within twenty-four hours after the intraperitoneal injection of bile. Baltaceano and Vasiliu³ ascribed the hypotension after the intraperitoneal injection of bile to the direct effect on the heart. Emerson⁴ caused a fall in blood pressure, arrhythmia, and cardiac standstill in dogs following the intravenous injection of whole bile or bile salts. Horrall and Carlson⁵ believed that bile salts act on the vagus endings and also directly on the myocardium through the coronary circulation. Regan and Horrall⁶ noted a fall in blood pressure in dogs following the intravenous injection of sodium glycocholate. Still⁷ demonstrated experimentally that the intravenous injection of small amounts of bile acids caused a slight rise in blood pressure and that large doses produced a marked fall. Ries and Still⁸ decided that bile salts in small doses caused an increase in the irritability of the vagus endings in dogs, and that large doses blocked the same endings. Meltzer and Salant,⁹ working on rabbits, affirmed Still's findings. Buchbinder,¹⁰ working on puppies attributed the bradycardia experimentally produced to a reflex through the vagus. Baruk and Camus¹¹ believed that the bradycardia was due to bulbar intoxication. Wakim, Essex, and Mann,¹² working on denervated hearts (isolated) of rabbits, found that perfusion with preparations of bile salts and of whole bile resulted in a slowing of the heart rate, a diminution in the amplitude of contraction, and various cardiac disturbances (ventricular alternation, extrasystoles, and ventricular fibrillation). Working on dogs, they¹³ concluded that whole bile and bile acids injected intravenously produced the same hypotensive effect and cardiac changes (brady-

cardia and disturbances in rhythm) in the absence, as well as in the presence, of the cardiac autonomic nerves. Schaeter and Dworkin¹⁴ concluded that the characteristic depressor action of bile salts in the circulating blood is not essentially due to the inhibition of cholinesterase.

Infectious jaundice is a generalized infection and the cardiovascular manifestation may be due to another factor, the direct involvement of the myocardium. Dawson and Hume¹⁵ reported a case of spirochetal jaundice with paroxysmal auricular fibrillation. Marchal, Soulié, and Roy¹⁶ reported, in the same condition, transient prolongation of the P-R interval and abnormal T waves. Electrocardiographic changes (paroxysmal auricular fibrillation, transient prolongation of the P-R interval, and flattening or inversion of the T waves¹⁵⁻¹⁸) have been noted in cases of spirochetal jaundice. In Weil's disease, pathologic changes (parenchymatous and interstitial changes with nuclear swelling, chromatolysis, infiltration of the interstitial tissue by lymphocytes, and polymorphonuclear leucocytes) have been described in the myocardium. Other observers have noted perivascular cellular infiltration, vacuolization, loss of striation, and hyalinization of the muscle bundles, acute leptospiral vegetative endocarditis, spirochetes in the myocardium, and multiple hemorrhages in the pericardium, subepicardium, and myocardium.¹⁹⁻²⁷

EFFECT OF EXERCISE ON THE SIZE AND SHAPE OF THE T WAVE

Because it was suggested that the T-wave changes noted in the eleven cases of infectious jaundice might be due to changing heart rate, the eleven subjects were studied several months after recovery. Electrocardiograms were taken after a thirty-minute rest period and after twenty-five to thirty vigorous hops. The data of this study are summarized in Table IV. It can be seen that, after exercise, the T waves became smaller (in at least two leads) in nine out of the eleven cases. In one case there was no change. In one case there was an increase in two leads; the increase was most noticeable in Leads I and II.

In another group of eleven normal persons, the height of the T wave was lowered by exercise in six cases; in four cases the T wave was increased in amplitude; and in one case there was no change. Thus, in a total of twenty-two controls, including the eleven cases of the series here reported (after recovery), tachycardia lowered the T wave in fifteen and increased it in five. The effect of exercise on the T wave was studied by Wood and Wolferth,²⁸ and their conclusion was that exercise caused an elevation in some controls and a depression in others. Clough³⁰ and Levine et al.³¹ studied the electrocardiograms after the subcutaneous injection of epinephrine and found in most instances a decrease in the height of the T wave at the time of the maximum epinephrine effect. In the cases of jaundice, the T wave was reduced in amplitude although bradycardia was usually present. Therefore change in the heart rate was not responsible for the decrease in amplitude of the T deflection.

SUMMARY

1. In an epidemic of twenty-four cases of infectious hepatitis, eleven subjects were studied electrocardiographically at the height of the disease and after recovery.

2. In nine cases the T wave was depressed during the disease and became normal after recovery.

3. There was no correlation between the depression of the T wave and the height of the fever or the intensity of the jaundice.

4. A study of a control group of persons after exercise revealed a depression of the T wave (with acceleration of heart rate), thus showing that the bradycardia was not responsible for the electrocardiographic changes.

5. A review of the reports of experiments in which bile salts and whole bile were injected into animals revealed similar T-wave changes which were probably due to an effect either on the vagus endings in the heart or on the myocardium itself. The myocardial effect is probably important in cases of Weil's disease, as evidenced by the reported pathologic findings in the myocardium.

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A METHOD FOR THE CONSTRUCTION OF THE VECTORCARDIOGRAM FROM THE EINTHOVEN ELECTROCARDIOGRAM

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THE term "vectorcardiogram" was applied by Wilson and Johnston¹ to a kind of record which shows in a single tracing the variations of the electric field within the body during the heartbeat. The record is made by means of a cathode-ray tube so connected to the Einthoven limb electrodes that the potential differences at the surface points combine to control the electron beam in such a way that the movements of the light spot on the fluorescent screen represent the changes in the direction and intensity of electric force due to the heart's activity. During diastole, when there are no potential differences in the heart, the spot of light remains stationary at the center of the screen. When activation of the heart muscle occurs and potential differences arise, the light spot is displaced to a succession of new positions which represent by direction and distance from the center the changing orientation and intensity of the electric field. The light spot finally returns to the center of the screen as the electric field fades at the end of the systole. The tracing consists of two loops of irregularly elliptical form, one being inscribed during the QRS period, the other during the T period. The latter is continuous with the former at a point which usually lies near the center of the screen. The electrical effects of auricular activity cause a similar but rather small displacement of the electron beam, but this effect, which is of less importance than is that produced by the ventricles, will be omitted from the present discussion. The movement of the light spot recorded on photographic film constitutes the vectorcardiogram. In this paper it will be referred to as the "VC." For examples of such records the reader is referred to Fig. 8.

During four years prior to 1940 the technique of vector representation of the heart's electric field was developed actively in Germany. By means of cathode-ray apparatus, connected to surface electrodes in one manner or another, several investigators²⁻¹⁰ produced records of different types and called by various names (Vektordiagramm, Triogramm, etc.) and had commenced a study of their clinical significance. In the comprehensive paper published early in 1940, Schellong⁵ reviewed the work of others and reported his own investigations, while the paper by Hollmann and Guckes⁹ dealt with the more important clinical interpretations, as well as with the technique.

It must be emphasized that the VC discloses nothing but that which is implicit in the electrocardiogram. When the potential differences between the electrodes in each lead are recorded separately, the electrocardiogram is pro-

duced. If, on the other hand, these three potential differences are combined suitably by instrumental means, the result, a VC, is a unitary record to which each of the three leads makes a contribution determined by the geometric relation of the lead to the actual electric field. In brief, the electrocardiogram may be said to analyze the field of electric force into three components, while the VC apparatus serves to recombine these components into a single unitary view of the field.

The true VC is, of course, a space curve, for the electric field of the body is extended in three dimensions in space; but, since the electrocardiogram is derived from potential differences measured only in the frontal plane of the body, the VC is a frontal plane projection of the true spatial VC. It is possible to derive the spatial VC by means of special records made by the cathode-ray apparatus and viewed stereoscopically. The German investigators previously referred to gave much attention to this stereoscopic technique and produced an interesting and probably important type of record. However, this phase of vectorecardiography will not be considered here since our concern is merely with a method of translating the electrocardiogram into the related frontal plane VC.

Since the VC is a product of the instrumental synthesis of the potential differences occurring in the three electrocardiographic leads, it is to be expected that the same curve could be derived by analytic or graphic treatment of quantities given by measurements made on the electrocardiogram. The object of the present paper is to describe a method by which this translation of an electrocardiogram into a VC may be made graphically with a minimum of effort and time, yielding a useful approximation to the exact VC.

In 1920, Mann¹¹ described the mathematical relationship between the electrocardiogram and a constructed curve, called by him a "monocardiogram," representing the variation of the electric field during the heartbeat. I believe Mann was the first to employ a tracing of the terminus of the changing vector to represent the successive vectors themselves, although Lewis, several years previously, and perhaps others before him, had employed diagrams picturing the vector at successive instants by means of lines radiating from a common center like the ribs of a fan. Mann's method provides a tracing which faithfully represents the vector changes, but the technique is tedious and time-consuming. Mann, himself, stated that the drawing of one monocardiogram "involved many hours of careful work," and it is probable that the neglect of his method has been due to the impracticability of employing the method in numerous cases, rather than to doubt about the value of the information that might have been derived. The method to be described here has been developed in the hope that its facility may lead to frequent employment and to discovery of meaning in the VC not apparent in the electrocardiogram. The possible usefulness of the VC method can be tested adequately only by its application to a large number of cases, and for this a facile method is needed. No doubt the cathode-ray apparatus, connected through the network devised by Wilson, provides the ideal means, but the apparatus at present is available only to a few

investigators. However, in one respect, the constructed VC has an unique advantage over the recorded VC: the analysis may be applied to electrocardiograms of selected types chosen from the store of existing records, and thus the investigator rapidly may accumulate data which may be treated statistically.

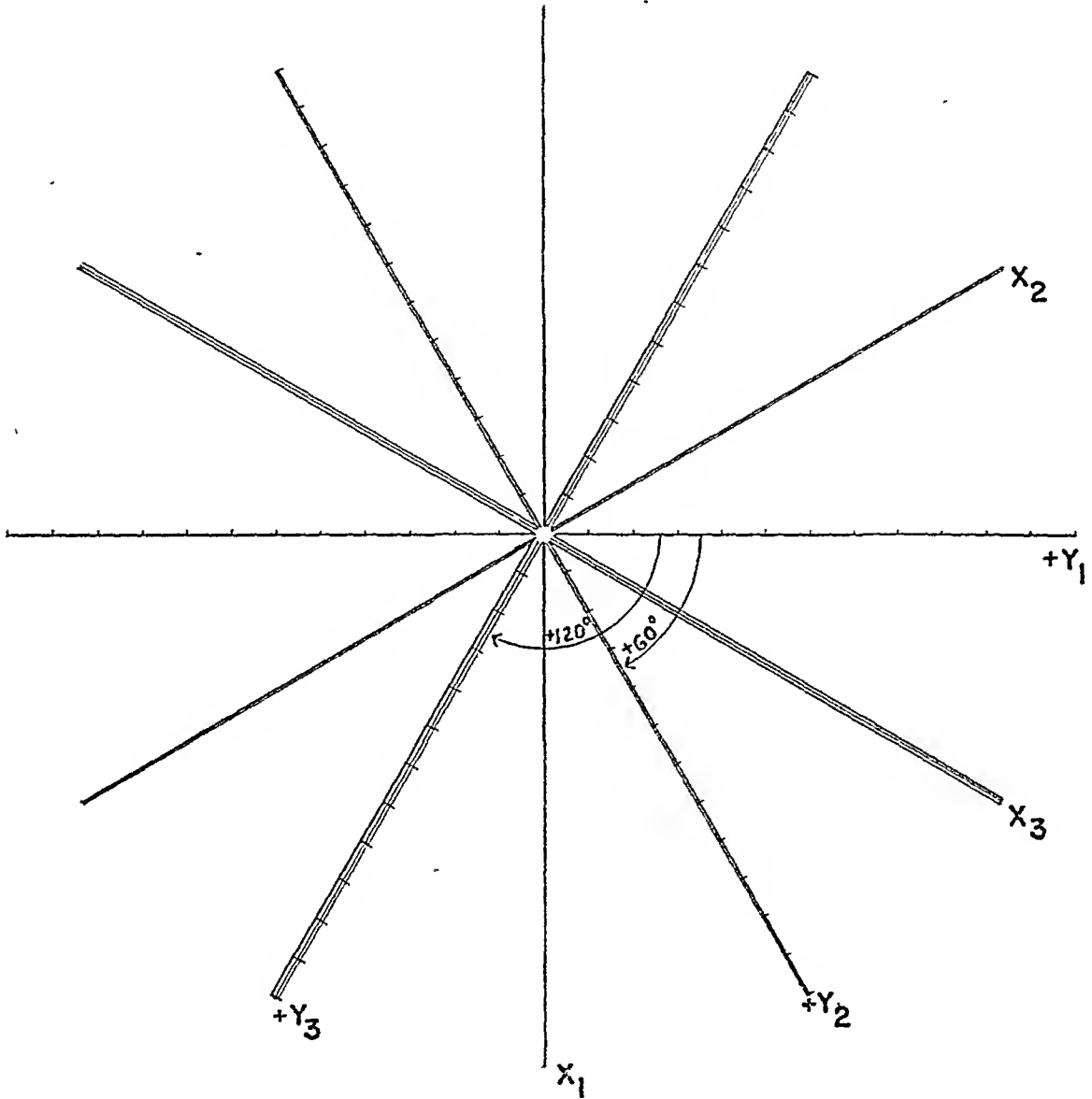


Fig. 1.—The threefold reference system. Each x axis divides the whole field into a positive and a negative half for the plotting of positive and negative potentials recorded in the respective lead tracings. The positive and negative y axes serve for the measurement of the departure of the QRS and T loops from the respective x axes. Scale on y axis: 1 unit = 0.1 millivolt.

THE METHOD OF CONSTRUCTING THE VECTORCARDIOGRAM

The principle of the method of construction is implicit in the well-known diagrams, published by many authors, showing the relation of the three lead tracings to the vector of the electric field framed in the Einthoven equilateral triangle. It is unnecessary here to attempt a justification of the Einthoven hypothesis in order to give validity to the VC. It is not claimed that the VC is a true graph of vector behavior; it is no more than an integrated view of the electrocardiogram. The integration, it is true, is based on the

Einthoven assumptions, but, even if these assumptions do not correspond closely to the facts, the hypothesis may be adopted arbitrarily as a means of arriving at a unitary view of the three electrocardiographic leads, which then may be correlated usefully with pathologic states and processes of the heart.

The frame of reference within which the VC is to be drawn consists of six lines intersecting at a common point, the origin, and separated by angular intervals of 30 degrees. These six lines, grouped in three pairs, form three overlapping reference systems, each of which serves for the representation of the potential differences recorded by one of the three leads of the electrocardiogram (Fig. 1). Distances and angles in this reference frame will be called positive or negative in a sense conforming with long-established electrocardiographic practice. Thus, distances measured to the right or downward will be called positive, while those measured in the opposite direction will be considered negative. Angular intervals measured clockwise will be called positive, while those that are measured counterclockwise will be considered negative.*

The co-ordinate axes for Lead I are the horizontal at 0° and the vertical at 90° . The vertical line serves as an x_1 axis, and distances measured from this line to the right represent positive potentials found in Lead I, whereas negative potentials are plotted to the left of the vertical. Distances from the x_1 axis may conveniently be measured along the horizontal by means of a scale marked upon it, 1 cm. on the scale representing 0.1 mv., or 1 mm. on a correctly standardized electrocardiographic tracing. The horizontal properly may be called the y_1 axis, for it is along this axis that the ordinates, or amplitude values of the electrocardiographic tracing, are measured. The x_1 axis, at 90° , bears no scale, for there is no electrocardiographic quantity requiring representation in this direction. The x_1 axis serves, however, to divide the whole field into a positive and a negative half with respect to Lead I. The second lead potentials, if positive, are represented by distances measured downward and to the right of the field from the x_2 axis at 150° in the direction of the y_2 axis at 60° . Negative potentials in Lead II are, of course, measured from the x_2 axis in the opposite direction. Lead III potentials are represented similarly by reference to the x_3 axis at 30° , positive and negative potentials being measured off from the x_3 axis in the 120° and the -60° directions, respectively. Although these three coordinate systems overlap, each is independent of the others and singular to the lead which it serves.

For some purposes it is desirable to define points on the VC by means of the ordinary rectangular co-ordinates. For this purpose the horizontal at 0° serves as a positive x axis, while that at 90° serves as a positive y axis.

*It seems inadvisable, in electrocardiographic studies, at this time, to adopt the mathematical convention whereby angular intervals that are extended counterclockwise are called positive. The wide adoption of this so-called English system by mathematicians and physicists probably was due to its adaptability to the mathematical treatment of electromagnetic phenomena, developed especially by English physicists; but this argument seems to have little weight in electrocardiographic studies. It perhaps is not widely known that the French system has no universal sanction; French mathematicians formerly called clockwise motion positive, or were eclectic in the matter, choosing whichever designation suited the purpose in hand. It may be that the English system serves better when the treatment of electrocardiographic problems is extended into the field of mathematical physics, as in some of the writings of Wilson and of Bayley, but for the simpler analyses, such as those of this paper, the system which was employed by Einthoven and, since then, has been in general use, seems better suited. Since the mean vector in normal cases is directed downward it is convenient and natural to use the positive sign for angular intervals measured downward from the horizontal axis.

It will be seen at once that this method of representing electrocardiographic potentials is strictly consistent with the Einthoven scheme. The y_1 (0°), y_2 (60°), and y_3 (120°) axes are parallel, respectively, to the three sides of the equilateral triangle. Positive angular intervals are measured clockwise from the horizontal axis and positive potentials are measured in the 0° , 60° , and 120° directions.

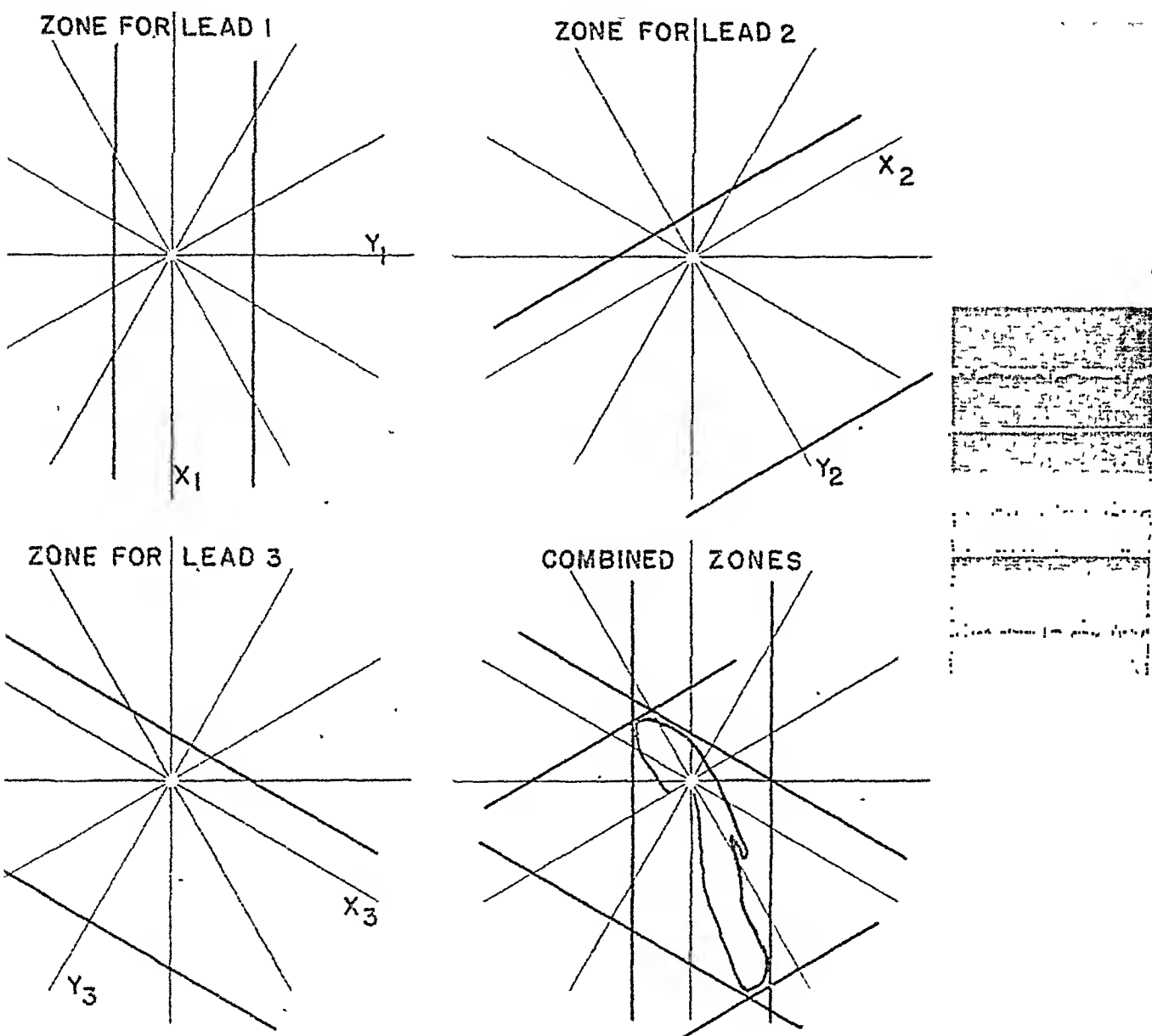


Fig. 2.—The composition of the polygonal envelope of the QRS loop is effected by combining the three zones that define the potentials recorded in the respective leads.

The approximate VC is drawn in this co-ordinate system in the manner now to be described. The equipment necessary for the work is simple. Two draftman's triangles, each having angles of 30° , 60° , and 90° are needed. The origin should be placed somewhat to the left of the center of a sheet of paper 8 by 10 inches. The six axes are readily drawn by suitable manipulation of the triangles. The y axes should be graduated in centimeters, each centimeter representing 0.1 millivolt. If much work is to be done time is saved by the use of

micrographed forms. Dividers may be used to measure amplitudes in the electrocardiogram, but this is not necessary since visual estimates give as much precision as the work calls for.

The maximum positive and negative voltages of the QRS complex in each lead tracing are measured and plotted as points on the proper y axes. Through each of these points a line is drawn at right angles across the y axis (Fig. 2). For each lead there will be two such lines. Each pair of lines defines a zone the length of which is unlimited but whose lateral boundaries represent the positive and negative limits of amplitude shown in the respective electrocardiographic lead. Therefore, the VC must lie within each zone and be tangent to the lateral boundaries of each. Consequently, the VC must lie in the area common to the three zones and be tangent to each of its boundaries. This common area is a six-sided polygon, constituting an envelope of the VC. Although the tangent points are not defined, the polygon, nevertheless, reveals the general shape of the VC and its orientation in the field. An enveloping polygon outlining the T loop is to be constructed in the same manner.

The VC might be defined more closely if the maximum and minimum potentials along other axes also were to be recorded by the electrocardiograph. It is possible to accomplish this by a simple maneuver (Fig. 3). If the electrode on the left arm and that on the left leg are connected through a resistance of, say, 5,000 ohms the potential at the mid-point of the resistance will be equal to the mean of the potentials at the left arm and the left leg. Now, if the mid-point be connected through a galvanometer with the right arm electrode, an electrocardiogram may be recorded which represents proportionally the difference in potential along an axis midway between that of Lead I and Lead II, that is, an axis at 30° . The magnitude of the voltages recorded will be somewhat less than that appropriate to a true 30° lead, but the full theoretic values for a 30° lead may be obtained by multiplying the recorded voltages by the factor $2/\sqrt{3}$, or 1.15. Similarly, a pseudo- 90° tracing may be made by connecting the mid-point of a resistance between the right and the left arm through the galvanometer to the left leg. A third interpolated lead, recording the proportional voltage in the 150° direction, requires a resistance between the right arm and the left leg and a connection from its mid-point through the galvanometer to the left arm. If, now, the maximum and minimum potentials recorded by these interpolated leads be measured and each multiplied by 1.15, the three pairs of values so obtained may be used to locate six more sides to be added to the polygon enveloping the VC. The twofold increase in the number of sides increases the accuracy with which the VC may be drawn, but this accuracy is gained only at the cost of time and effort when the electrocardiogram is recorded, so that the method probably would not be acceptable for clinical routine but only for special studies.

The VC now is traced within the polygonal envelopes constructed for the QRS complex and for the T wave, respectively. The QRS loop is begun at the center of the field and continued as a smooth curve, grazing in succession each side of the polygon. The method does not provide any simple means of determining the tangent points on the six sides, but some considerations which may serve

as a partial guide will be mentioned later. An acquaintance with the patterns of recorded VC loops published by Wilson and Johnston¹ (Fig. 8) can be of assistance. The QRS loop ends at the origin or at a near-by point, the location of which is discussed below. From this point the T loop is drawn in like manner within the small polygon previously drawn to represent the maximum and minimum voltages of the T deflection. As will be apparent later, the direction of motion of the vector is of importance, but the form of the VC is in-

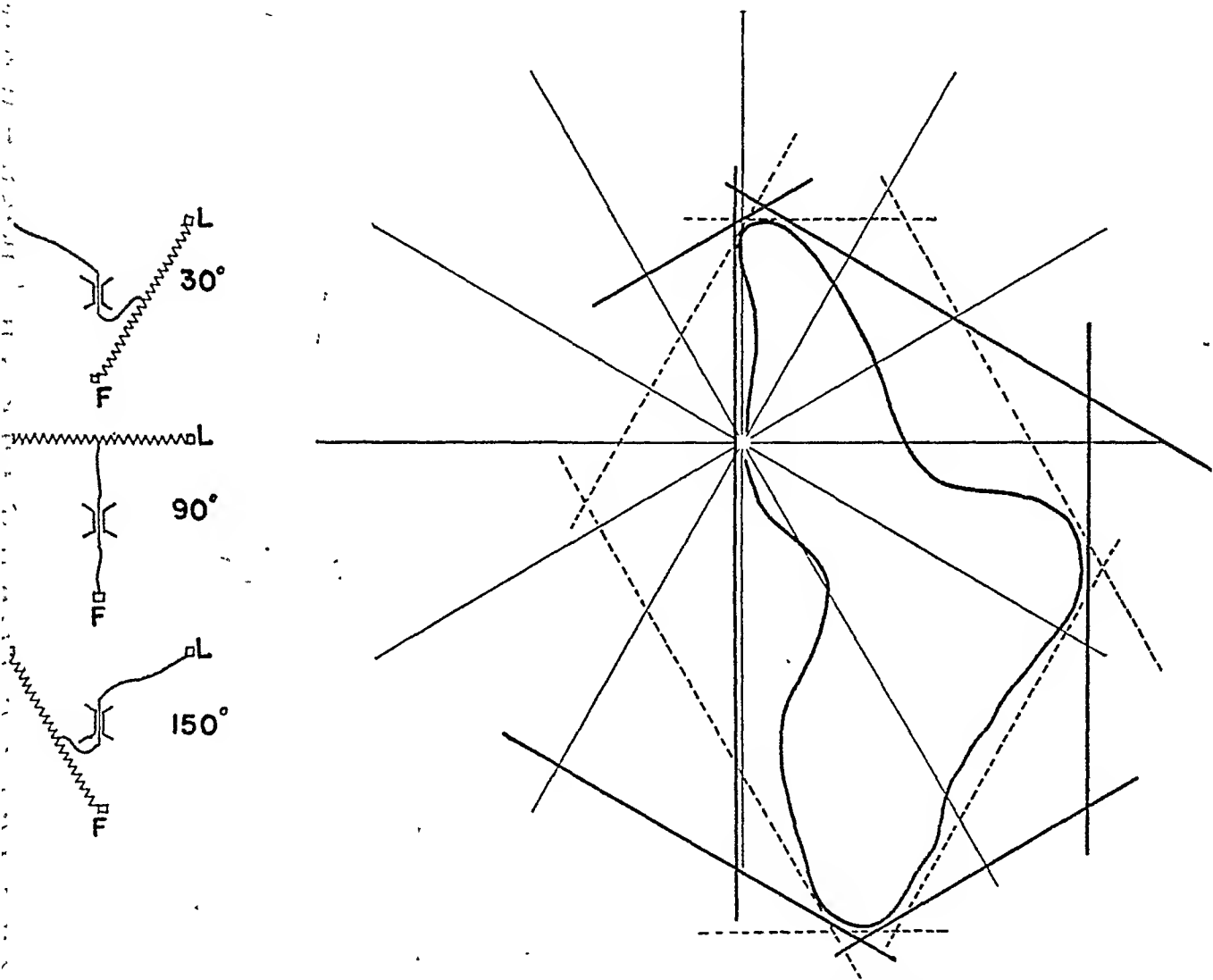


Fig. 3.—The twelve-sided envelope for the QRS loop is formed by adding to the basic polygon six lines representing the potential limits recorded by means of *interpolated leads*.

dependent of the direction in which it is traced. Hence the curve should be drawn either clockwise or counterclockwise, as appears convenient. The direction of rotation then can be determined by methods which will be explained in a later section.

The point at which the end of the QRS loop joins the beginning of the T loop is of considerable importance. It will be referred to as *J* (for junction). The corresponding point in the electrocardiogram also will be called *J*.*

*The symbol *J* might well be substituted in electrocardiographic terminology for the official term "R-T junction" or for terms inspired by an excess of zeal for precision, such as "the R-T or S-T junction as the case may be," a designation actually used by one author. The thing to be designated is only a point, and should be indicated by a letter; the component of QRS which ends at the point should be omitted from the general term used to indicate the point.

To locate J in the vector field the position of J in each electrocardiographic lead first is identified and then its displacement from the zero level is measured. This procedure sometimes is difficult on account of the ill-defined transition of the QRS complex to the T deflection, or because of uncertainty of the zero level, or, again, because of the variability of the complexes due to respiratory or other less obvious causes. But, if care is taken, the result will be found very nearly to satisfy Einthoven's summation equation, $e_2 = e_1 + e_3$. Turning now to the VC field, a point is selected on each of the three y axes corresponding to the respective potentials of J in the electrocardiogram. Through each of these points a line is drawn perpendicular to its proper y axis. If the displacements of J in the electrocardiogram have been measured correctly the lines will intersect at a point, a necessary consequence of the summation equation; but more often they will form a small equilateral triangle the size of which will be proportional to the errors in measuring the displacement of J in the electrocardiogram. If the triangle is small a point at its center may be taken as the approximately correct position of J .

The VC, having been sketched in roughly, should be scrutinized, segment by segment, to see if it is, in all parts, consistent with the potential changes revealed by the electrocardiogram. It is obvious that, where the potential is increasing in a segment of one lead, the departure of the corresponding segment of the VC from the x axis proper to that lead also must be increasing. But it is necessary that this representation of the sign and rate of change of potential should be true with respect to all three leads simultaneously. If it were possible perfectly to fulfill this requirement the VC would be a quite faithful representation of all that is shown in the electrocardiogram, but, of course this ideal result is beyond reach. However, it will be found that the simultaneous control of the path of the VC by three leads is not too difficult to visualize and that, with a little practice, the roughly sketched VC can be rectified to yield useful results.

Theoretically, notching and slurring of QRS can be represented in the VC, but it was found in practice that such representation was not very satisfactory when compared with the cathode-ray record. Unless the faulting is very coarse it is better to neglect it. Whether or not this limitation is a desideratum from the clinical standpoint cannot well be judged until the clinical meaning of short-period variations of potential are better understood.

THE DEVELOPMENT OF DETAIL IN THE CONSTRUCTED VC

A study of the mathematical relationship of the VC to the electrocardiogram reveals several additional characteristics of the loops that may be deduced from the Einthoven record. First, it is possible by rather simple means to determine the direction of the VC curve in any particular segment, and thus to correct the roughly drawn loop to any desired extent, within modest limits. Second, the direction in which the loop is inscribed may be determined with certainty in most cases. Third, the velocity of inscription of particular segments may be determined approximately. All these characteristics may be determined by Mann's method, but that technique seems too burdensome to be acceptable. New

methods will be described here by which these details may be revealed, and it is believed that the methods are facile enough to commend themselves to anyone not averse to a little computation.

It must be acknowledged that no great accuracy can be obtained by these methods, but it is thought that the approximation can be made close enough to give results of some practical value. Accuracy is unobtainable primarily because the time element, clearly expressed in the electrocardiogram, is largely submerged and lost in the process of constructing the VC, so that it is impracticable to identify on the VC a point representing a particular time instant on the electrocardiogram. However, it is possible to correlate segments of the VC with nearly simultaneous segments of the electrocardiogram. Thus, early, middle, and late segments of the excursive (outgoing) limb of the VC loop readily are correlated with corresponding segments of the ascending limb of the electrocardiographic deflection, and as one becomes accustomed to the technique, the simultaneous segments may be defined with increasing confidence. Another characteristic of the ordinary electrocardiogram makes great accuracy unobtainable; the record made by a galvanometer with only one string necessarily requires that the three leads be recorded in succession, and thus one does not have a first and second lead record of one particular heartbeat; consequently when a second lead deflection is paired with another in the first lead it is by no means certain that the two are strictly congruous.

DETERMINATION OF THE SLOPE OF A SEGMENT OF THE VC

To determine the direction, or slope, of a particular segment of the VC use is made of an electrocardiographic characteristic which, I believe, previously has not been considered in electrocardiographic studies, i.e., the slope of the electrocardiographic tracing at a particular point. It can be shown that the slopes at simultaneous points on the tracings of two electrocardiographic leads determine the direction, or slope, of the corresponding segment of the VC. The mathematical analysis disclosing this relationship follows immediately. We assume that the approximate VC has been drawn. For the rectification of a particular segment it is desired to find the average slope of the curve in that region. The slope of the VC at any point is that of the tangent with reference to the horizontal and vertical axes constituting the x and y axes of a rectangular co-ordinate system. The tangent may be expressed as y/x , but since the direction of the curve is continually changing we will express the slope by the differential notation dy/dx . In the analysis the following symbols also will be used.

E_m , the magnitude of the vector at any point on the VC.

e_1 and e_2 , the amplitude (voltage) of the electrocardiographic tracing in Leads I and II, respectively.

de_1 and de_2 , differentials standing for the slopes of the electrocardiographic tracings at corresponding points in Lead I and Lead II.

x the distance of any point on the VC from the vertical axis.

y the distance of any point on the VC from the horizontal axis.

α the angle between the vector and the horizontal axis at any instant.

t time as measured on the electrocardiographic tracing.

The analysis begins with the familiar equations of Einthoven,

$$e_1 = E_m \cos \alpha \quad (1)$$

$$e_2 = E_m \cos (60^\circ - \alpha) \quad (2)$$

From these we derive equations giving the value of x and y in terms of e_1 and e_2 with the angle α eliminated. From the definitions and from the construction it is evident that

$$x = e_1 \quad (3)$$

From Equation 2, by suitable transformation* we have

$$y = \frac{1}{\sqrt{3}} (2e_2 - e_1) \quad (4)$$

By differentiation of Equations 3 and 4, with respect to time, we obtain

$$\frac{dx}{dt} = \frac{de_1}{dt} \quad (5)$$

$$\frac{dy}{dt} = \frac{1}{\sqrt{3}} \left(\frac{2de_2}{dt} - \frac{de_1}{dt} \right) \quad (6)$$

Dividing Equation 6 by Equation 5 and replacing $\frac{1}{\sqrt{3}}$ by 0.58

$$\frac{dy}{dx} = \frac{1}{\sqrt{3}} \left(\frac{2de_2}{de_1} - 1 \right) \quad (7)$$

By similar steps, employing the slopes measured in Lead I and Lead III, we obtain

$$\frac{dy}{dx} = \frac{1}{\sqrt{3}} \left(\frac{2de_2}{de_1} + 1 \right) \quad (8)$$

and from Lead II and Lead III,

$$\frac{dy}{dx} = \frac{1}{\sqrt{3}} \left(\frac{de_2 + de_3}{de_2 - de_3} \right) \quad (9)$$

*The steps in the transformation are as follows: By the standard formula for the cosine of the difference of two angles Equation 2 may be written

$$e_2 = E (\cos 60^\circ \cos \alpha + \sin 60^\circ \sin \alpha)$$

$$\text{or } e_2 = \frac{1}{2} E \cos \alpha + \frac{\sqrt{3}}{2} E \sin \alpha$$

$$\text{Transposing, } \frac{\sqrt{3}}{2} E \sin \alpha = e_2 - \frac{1}{2} E \cos \alpha$$

$$\text{Dividing by } \frac{\sqrt{3}}{2} \text{ and factoring,}$$

$$E \sin \alpha = \frac{1}{\sqrt{3}} (2e_2 - E \cos \alpha)$$

From the construction, $E \sin \alpha = y$, while by Equation 1 $E \cos \alpha = e_1$

$$\text{Hence by substitution, } y = \frac{1}{\sqrt{3}} (2e_2 - e_1)$$

Method of Using the Slope Equations.—Any one of the three pairs of leads may be used for the determination of the slope of a particular segment of the VC, but, usually one pair is best suited for measurement; this should be chosen, and the proper equation used. The slope of the electrocardiographic tracing at a selected point may be measured easily in the following manner (Fig. 4): The straight edge of a piece of paper is placed accurately tangent to the tracing at the selected point. A small protractor is then placed so that its base edge coincides with any convenient horizontal line of the electrocardiographic grid, the center mark of the protractor being placed at the edge of the paper. Then,

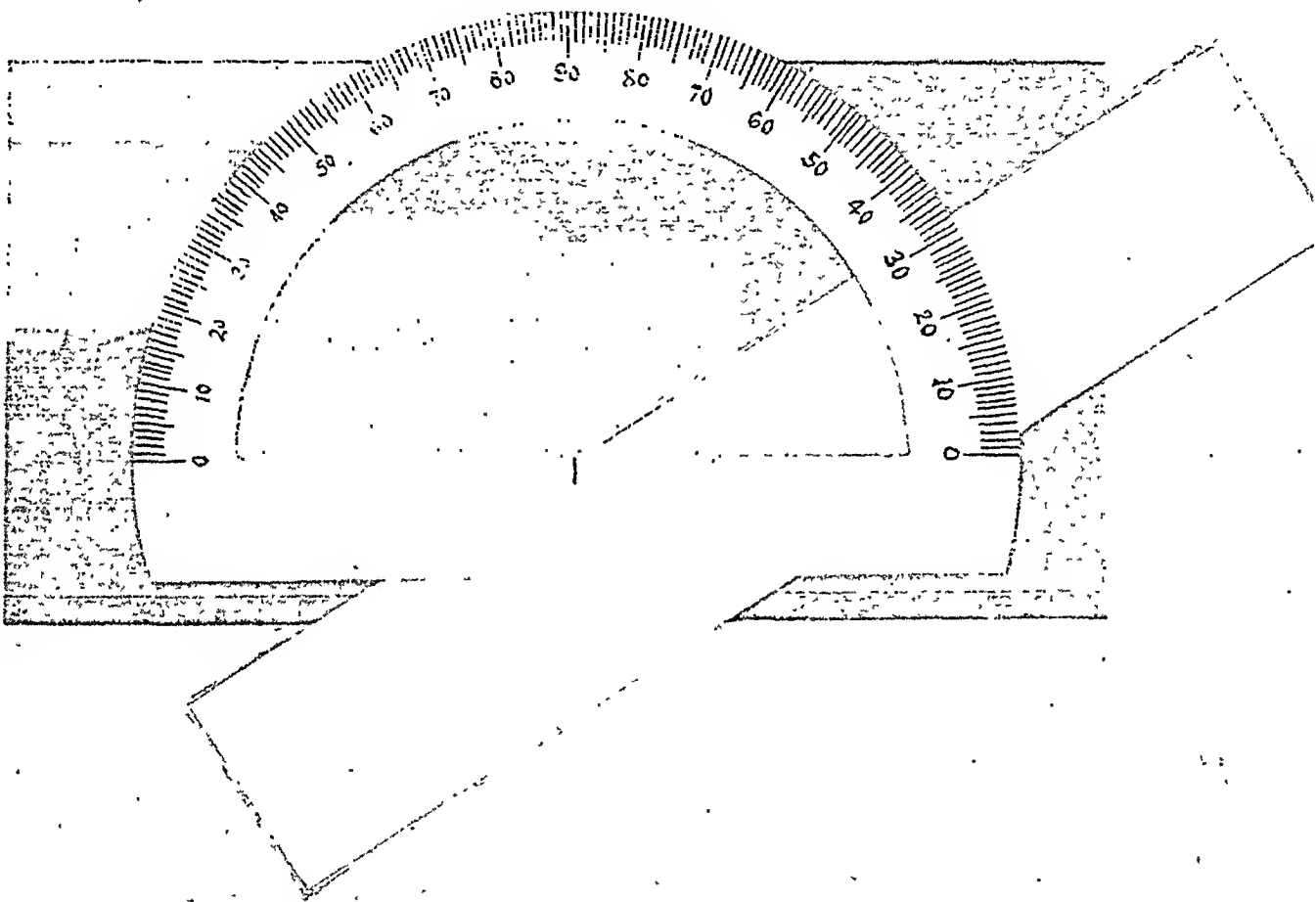


Fig. 4.—Showing the method of measuring the slope of a segment of electrocardiographic tracing by means of a protractor and a paper straightedge.

on the scale of degrees, the angle between the edge of the paper and the horizontal grid line is read off. A table of trigonometric functions is used to find the tangent of the angle, that is, the slope of the electrocardiogram at the point in question. There remains only the substitution of the values found in the two leads for the differentials in the proper slope equation (Equation 7, 8, or 9) and completion of the indicated calculation. The result is the slope of the tangent to the VC. Usually it will be convenient to find the angle represented by the tangent and to use the angle to indicate the direction of the curve.

From the slope equations simple relations may be deduced by means of which it is practicable roughly to determine the slope of the VC without the use of measurements or calculations, the necessary data being obtained by mere

inspection of the electrocardiogram. These relations are set forth in Fig. 5. The diagram provides data for a rough check on the correctness of the value of the slope obtained by measurements and calculation, but, more especially, it is useful for revising the original rough sketch of the VC.

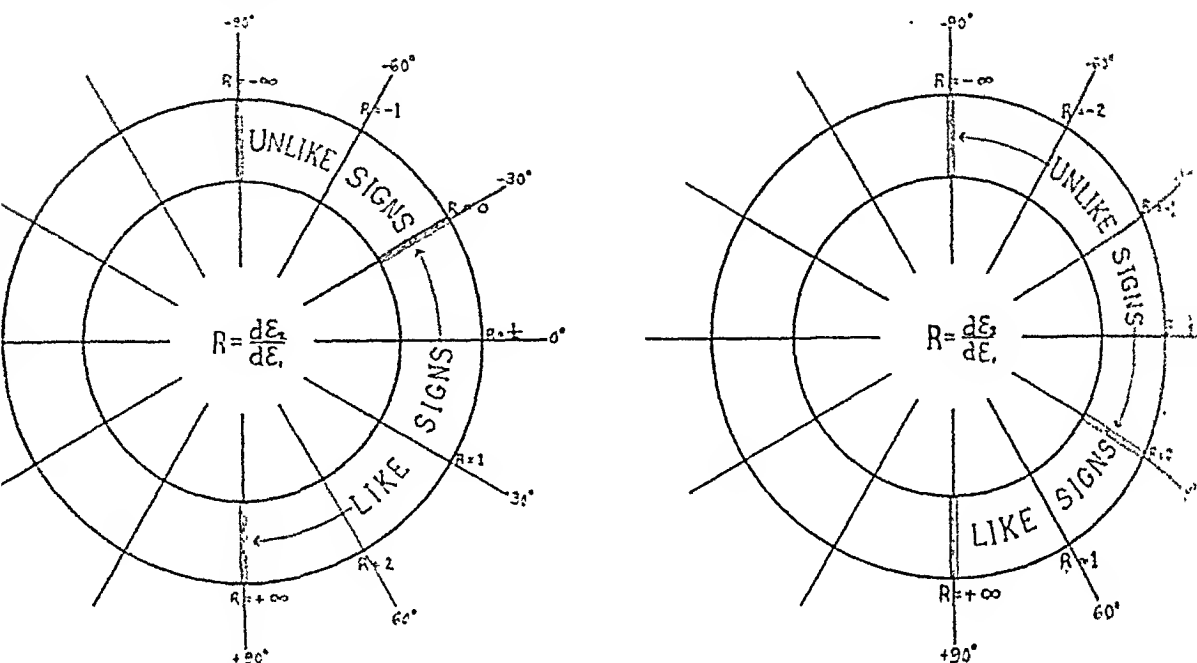


Fig. 5.—Diagrams for the rough estimation of the slope of a segment of the VC. The diagrams show the slope, dy/dx expressed as angle, of a segment of the VC when the ratio, $d\epsilon_2/d\epsilon_1$ or $d\epsilon_3/d\epsilon_1$, has the indicated value. The ratios of the slopes of the electrocardiographic tracings are represented by the symbol R . The corresponding slope of the VC is shown in one or the other indicated sector depending on the sign of the ratio. The value of R varies continuously from $-\infty$ to $+\infty$. For approximate results intermediate values of R may be interpolated visually. Use of the diagram may be illustrated as follows: If the slope of segment of the electrocardiogram in Lead II is about twice as great as the slope of the corresponding segment in Lead I the $R = 2$; If the slopes of the segments of the electrocardiogram are both positive or both negative, then the slope of the corresponding segment of the VC will be shown in the first diagram by the radius in the sector of like signs where $R = 2$. This slope is 60° . These diagrams must not be mistaken for representations of the vector field with the radii as vectors of electric force; the radii represent merely the slope of a segment of the VC, and the segment in question may lie in any part of the vector field.

THE ROTATION OF THE VECTOR

It seems probable that the sense of rotation of the VC* is a significant characteristic of the vector motion and that methods for its recognition may be useful in clinical diagnosis. But it is obvious that a more fundamental characteristic of vector behavior is the rotation of the spatial vector, and the question arises, to what extent does the apparent rotation in the frontal plane reflect the true motion of the vector in space. On consideration it will be seen that the true motion in space cannot be deduced from the apparent motion in the frontal plane. To make this fact obvious, let us assume that the spatial loop lies throughout its extent in one plane, that the generating point rotates continuously in one direction and that the frontal plane projection of the generating point appears to rotate clockwise. Now let the plane of the spatial loop be turned on an axis that lies within the plane and also passes through the origin, until the

*The terms sense of rotation and direction of rotation of the generating point or of the VC will be used interchangeably and with identical meaning. Clockwise rotation will be called positive; counter-clockwise rotation will be called negative.

plane of the loop is perpendicular to the frontal plane. The projected loop will appear to become narrower, but without change in the sense of rotation, until the plane of the spatial loop reaches a position perpendicular to the frontal plane. As the turning is continued the projection in the frontal plane again appears as a loop, but the sense of rotation now will be counterclockwise. Hence we are forced to the conclusion that, if a slight change in the orientation of the spatial loop without other change in the character of the true vector motion causes the rotation of the VC to change from positive to negative, the sense of rotation in our constructed VC cannot be regarded as of certain and fundamental significance. There remains, however, the possibility that a study of the VC may show tendencies for changes in rotation to be correlated with states of the myocardium. Already it is apparent that in the normal heart the frontal projection of the QRS vector rotates clockwise in nearly all cases, while rotation in the opposite direction is common in cases of left ventricular hypertrophy or when there exists well-marked counterclockwise rotation of the heart on its longitudinal axis, such as is common in hearts occupying a transverse position.

When the cathode-ray apparatus is more generally available it is likely that the stereoscopic method will enable us to explore the meaning of the true motion of the spatial vector, but in the meantime there is an opportunity to search for provisional meanings in the constructed VC and thus to prepare for the more intimate study by more adequate means.

By methods which will be described it has been found practicable to recognize the sense of rotation of the generating point of the constructed VC with a fair degree of certainty in a considerable proportion of records. However, there is one type of record in which it is futile to attempt recognition. When a loop is very narrow and straight the curvature is too slight to permit recognition. This type of loop appears when the electrocardiogram shows in one lead a very slightly developed deflection, as in the approximately isoelectric T wave.

RECOGNITION OF SENSE OF ROTATION OF LOOP

The sense of rotation of the QRS loop usually can be recognized by mere inspection of the tracing. The loop almost always lies to some extent on both the positive and the negative sides of the x axis of one of the leads. In this case the electrocardiogram is diphasic in that lead and then the order of succession of the positive and negative phases of the deflection indicates the order in which the positive and negative halves of the vector field are traversed by the generating point (Fig. 6). The diphasic character most often is shown by the third lead tracing, but when no single lead gives a clear indication a decision often can be reached by taking account of a concurrent indication found in another lead.

In the case of the T loop, judgment is more difficult, for in the majority of records the T deflection is not diphasic in any lead. However, there are several special methods by one or more of which a conclusion usually can be reached. Three methods will be described; they will be arranged in the order of facility of application. Each of the methods, though sound in principle, may fail in certain cases. Usually it is best to employ more than one method and to accept the consensus.

First Method.—If the T wave is definitely diphasic in one or more leads, the sense of rotation can be recognized at once by application of the same principle as in the case of the diphasic QRS complex.

Second Method.—It may be seen by reference to any of the constructed VC's reproduced with this report that the generating point for either the QRS

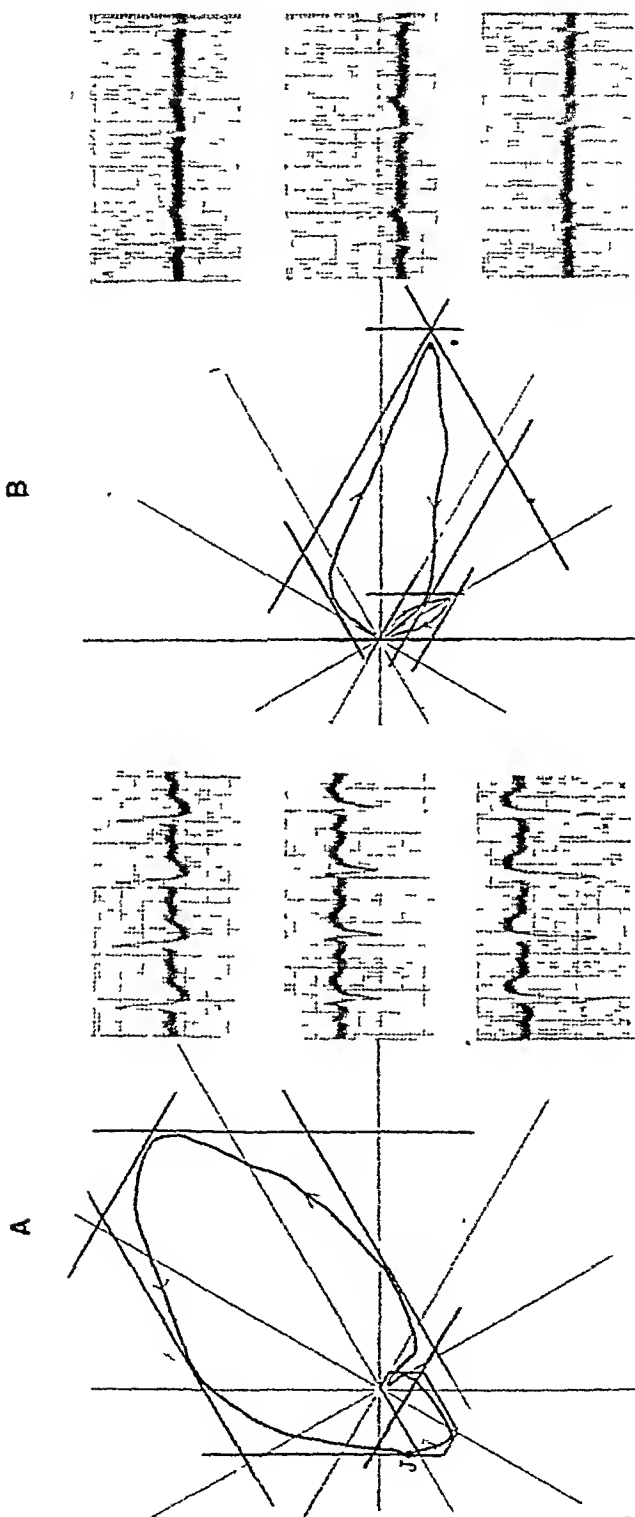


Fig. 6.—The two electrocardiograms, with their constructed VC's, are presented to illustrate the methods described in the text for determining the sense of rotation of the T loop. The scale for the QRS loop in B is reduced to one-half that employed for the T loop.

or the T loop, moving clockwise, reaches the positive boundaries of the enveloping polygon in the order: Lead I, Lead II, Lead III. If the rotation is counterclockwise this order is reversed. The modification of the rule for the case of maximum negative deflections is obvious. If then a T loop has been constructed from a particular electrocardiogram, the sense of rotation can be recognized if we learn the order in which the apices of the T waves were inscribed in two of the leads. In general, this can be determined by measuring the abscissas of the apices from simultaneous points in the two leads. In most records the apices of the R deflection, in the two leads where the R wave is highest, are very nearly simultaneous, the phase difference usually being less than 0.01 second (0.25 mm. with the usual recording speed). Consequently the apices of the R deflections usually may be taken as fairly reliable zero points for measuring the time interval to the apices of the T wave. But unless the phase difference of the two apices is found to be rather more than 0.25 mm., the significance of the measurement will be in some doubt and a conclusion as to which is the leading T wave should be made with some reserve. The conclusion can be tested by employing either the beginning or end of the QRS deflection as a base point, but these positions often are deceptive and their identification should be made with care after selecting complexes in which the breakaway point is clearly defined.

Third Method—The Curvature Test.—This test has proved to be very easily applied, requiring little more than mere inspection of the electrocardiogram. Unfortunately a somewhat involved explanation scarcely can be avoided if the principle is to be set forth adequately.

If the vector is turning clockwise, the slope of the VC continuously increases. This remains true in whatever quadrant the tangent to the VC may lie. If the slope is positive at the beginning of the loop it will assume increasing values until 90° is reached, where the value is infinite. As clockwise rotation is continued, the slope becomes negative but of large absolute value. Then smaller absolute values follow, but since they are negative they are, in fact, increasing. The same holds true throughout the full circle. Contrariwise, if the rotation is continuously counterclockwise the slope of the tangent diminishes continuously. If a function is increasing, its derivative is positive; if decreasing, its derivative is negative. Therefore we can learn whether dy/dx is increasing or diminishing at a given point on the curve by obtaining the derivative of that function and noting its sign. Since the function of which we seek the derivative is itself a derivative of y with respect to x , the result of the differentiation is the second derivative of y with respect to x . This will, as usual, be expressed by d^2y/dx^2 . Therefore, to find the sign of d^2y/dx^2 for a particular point on the VC, we write the derivative of the right-hand member of each slope equation. From Equation 7 the derivative is

$$\frac{de_1 d^2 e_2 - de_2 d^2 e_1}{(de_1)^2} \quad (7a)$$

From Equation 8 the derivative is

$$\frac{de_1 d^2 e_3 - de_3 d^2 e_1}{(de_1)^2} \quad (8a)$$

From Equation 9 the derivative is

$$\frac{de_2 d^2 e_3 - de_3 d^2 e_2}{(de_2 - de_3)^2} \quad (9a)$$

To determine whether the slope of the VC at a point is increasing or diminishing it is necessary only to know the *sign* of the second derivative. The sign of this function (Equations 7a, 8a, and 9a) is determined by the sign of the numerator in the parentheses, since the sign of the denominator in all cases must be positive. Now the sign of each term of the numerator can be recognized by mere inspection of the electrocardiogram. If the slope of the tracing is upward to the right, at the particular point selected for the test, de is positive, while a slope that is downward to the right makes de negative. If the slope runs horizontally de is zero. The terms $d^2 e_1$ and $d^2 e_2$ represent the rates of change of slope.* For our present purpose this function may be regarded as equivalent to "curvature." The sign of the curvature is positive if the tracing is concave upward and negative if convex upward. The sign of $d^2 y/dx^2$ now may be determined by noting the sign of the slope and of the curvature at the chosen point in each of two electrocardiographic tracings, and combining the signs algebraically. In practice it is convenient first to write the significant numerator of Equation 7a, 8a, or 9a by substitution of symbols that have a more obvious meaning. Using S for slope and C for curvature these expressions then read:

for Lead I and Lead II,	$S_1 C_2 - S_2 C_1$
for Lead I and Lead III,	$S_1 C_3 - S_3 C_1$
for Lead II and Lead III,	$S_2 C_3 - S_3 C_2$

These expressions will be referred to as the "curvature formulas." They are not the exact mathematical equivalents of the numerators in the parentheses in Equations 7a, 8a, and 9a, but, as previously explained, they serve as guides for combining the signs of the slopes and of the curvatures, resulting in a correct determination of the sign of the second derivative. The formulas are to be used in the following manner: Having selected corresponding short segments of the T wave in, say, Leads I and II, the signs of the slopes and curvatures are noted and written down in place of the symbols in the first of the curvature formulas. For example, in the electrocardiogram of Fig. 6, A, at a point about the middle of the S-T segment in Lead I both the slope and the curvature are positive, while in Lead II in the corresponding segment the slope is positive and the curvature is negative. Thus the signs, as written down, read $(+ -) - (+ +)$. In this case the sign of the whole expression is negative and the slope of the corresponding segment of the VC is shown to be diminishing, that is, the T loop is being traced counterclockwise.

*The rate of change of slope, sometimes called the "flexion" of the curve, is related to, but is not identical with, curvature. For an exact statement of the relation a textbook on calculus should be consulted. For the purpose of the present analysis it is sufficient to state two facts concerning the relation. First, the flexion ($d^2 e$) and the curvature always have the same sign. Second, if the slopes are equal in two curves, the flexions are proportional to the curvatures. For these reasons, in the use of the change of slope equations, no error will be introduced by assuming that the $d^2 e$ terms actually stand for curvature.

The availability of this procedure unfortunately is limited to a considerable extent by the fact that, if both terms of the formula are positive or both are negative, the resultant sign remains indeterminate without a knowledge of the absolute values of the S and C quantities, for, under this condition, the sign of the difference will depend on which term is the larger, and this we have no simple means of determining. However, there is one condition, easily recognized, under which this difficulty does not arise, and the success of the test is assured, namely, when the two slopes are of the same sign and the two curvatures are of opposite signs, or vice versa. In this case the two terms of the formula will have unlike signs and the relative magnitudes will not affect the sign of the difference.

There are two special cases, frequently occurring, in which the curvature formula may be applied with great ease. (A) If a point of zero slope can be found in one lead while at the corresponding point in the other lead the slope is not zero, then the formula reduces to one term and the sign of the whole expression is evident. This test readily may be employed in the analysis of the tracing in Fig. 6, A, where T_2 has zero slope at the point of maximum deflection while at the corresponding point in T_1 the slope is positive. In this case the formula, written with signs only, reads $(+ -) - (0 +)$. The whole expression, then, has a negative sign, thus indicating a counterclockwise rotation of the VC.

(B) As explained in the footnote on page 206, the magnitude of two curvatures properly may be compared when the slopes are equal. Hence we have the following rule: If a segment in one lead has a curvature sensibly greater than the curvature in the other lead, and, if in the corresponding segments the tracing of greater curvature has a slope at first less, and then greater, than in the other lead, it is obvious that at some point in the region of curvature the slopes will be equal. It is not necessary that this point be identified; the knowledge that it exists is sufficient. Since the greater of the C terms is known by inspection of the tracings and the S terms are equal at some point in the segment in question, the greater of the two terms of the curvature formula is obvious and the sign of the whole is readily found. Electrocardiograms in which this procedure is applicable are of frequent occurrence, and a record of this type is shown in Fig. 6, B. If points near the middle of the S-T segments of Lead I and Lead II of that record are examined it readily can be seen that at some point the slopes are equal and positive and that the curvature at that point in Lead II is greater than in Lead I, and that in each lead the curvature is positive. Hence $S_1C_2 > S_2C_1$ and the sign of the whole expression is positive. Therefore, the T loop in the segment in question is rotating in a clockwise direction.

The curvature test, of course, reveals the sense of rotation only of the limited segment to which it is applied, but usually it is true that the rotation obtaining in any considerable segment of the T loop will be found to prevail throughout. If T loops in the form of lunes, figures of eight or other more complicated figures were common, the determination of the direction of rotation at one, or even at two points could not be trusted, but such forms appear to be uncommon. Through the kindness of Dr. Mann I had an opportunity to search through a large number of his recorded monocardioagrams and failed to find an instance of a deceptively irregular loop; in all cases where the loops

were clearly inscribed they appeared as somewhat irregular ellipses each having a rotation, the sense of which was maintained throughout. It is desirable that this point be verified by means of VC's electrically recorded and made with reduced light intensity so that the form of the T loop may be recorded clearly throughout its full path.

THE VELOCITY OF INSCRIPTION IN A SEGMENT OF THE VECTORCARDIOGRAM

The electrocardiogram is a time-potential graph, but the process by which the VC is constructed eliminates the time factor from the result; therefore the time required for the generating point to trace out any given segment cannot be determined without a further analysis. In the case of the electrically recorded VC Wilson revealed the velocity of inscription by the ingenious device of interrupting the accelerating voltage through the cathode-ray tube at a known frequency, say two hundred interruptions per second. The effect of this was to make the tracing appear as a series of dashes the number of which per unit length of the curve indicated the velocity. It has seemed desirable to introduce the velocity characteristic into the constructed VC, and a practicable means to this end will be described.

The velocity of inscription in a chosen segment may be determined rather simply by the use of the following principle. If at any point in the VC the rate of increase of the distance of the generating point from the x_1 axis is known, and if the direction of motion of the generating point at that instant also is known, the linear velocity of inscription may be represented by the equation

$$ds = \frac{dx}{\cos \theta} \quad (10)$$

where ds stands for the linear velocity, dx for the horizontal component of that velocity, and θ for the angle between the horizontal and the tangent to the VC at the point in question. dx is essentially identical with the de_1 of Equations 7, 8, and 9, that is, it is the slope of the electrocardiogram in the corresponding segment. Heretofore, the slope of the electrocardiographic tracing has been expressed as angle or tangent of angle, but for the present purpose it conveniently may be expressed as millivolts per second. Unit slope may be taken as 45° , where the tangent is unity, and at this angle the rate of change of slope is 2.5 mv per second. Therefore, when the slope of the electrocardiogram at a chosen point in Lead I has been determined, the horizontal component, dx , of velocity may be found by multiplying 2.5 mv per second by the measured electrocardiographic slope. Then, to find $\cos \theta$, three steps are taken: (1) de_2 or de_3 is found by the use of the protractor and tables; (2) dy/dx , the slope of the VC in the corresponding segment is found by means of Equation 7, 8, or 9; and (3) the cosine of the angle represented by dy/dx is found in tables. With dx and $\cos \theta$ known, ds is found by substitution in the velocity equation (10). The measurements and calculations readily can be made in a few minutes, but, after a little practice, rough results may be obtained by means of visual estimates of the rate of change of voltage in the first lead and of the slope of the selected segment of the VC. When this method (with measurement and calculation)

was applied to the electrocardiogram and VC of Case 1 of Fig. 8 the rate of inscription of the excursion was found to be 9.1 mv per second while the velocity calculated directly from the recorded VC was 8.1 mv per second. The rate of recursion, determined by the method of this paper, was 4.9 mv. per second, while calculated directly from the recorded VC the rate was 4.1 mv per second. The correspondence of these results is close enough to indicate that the method may be useful for some purposes.

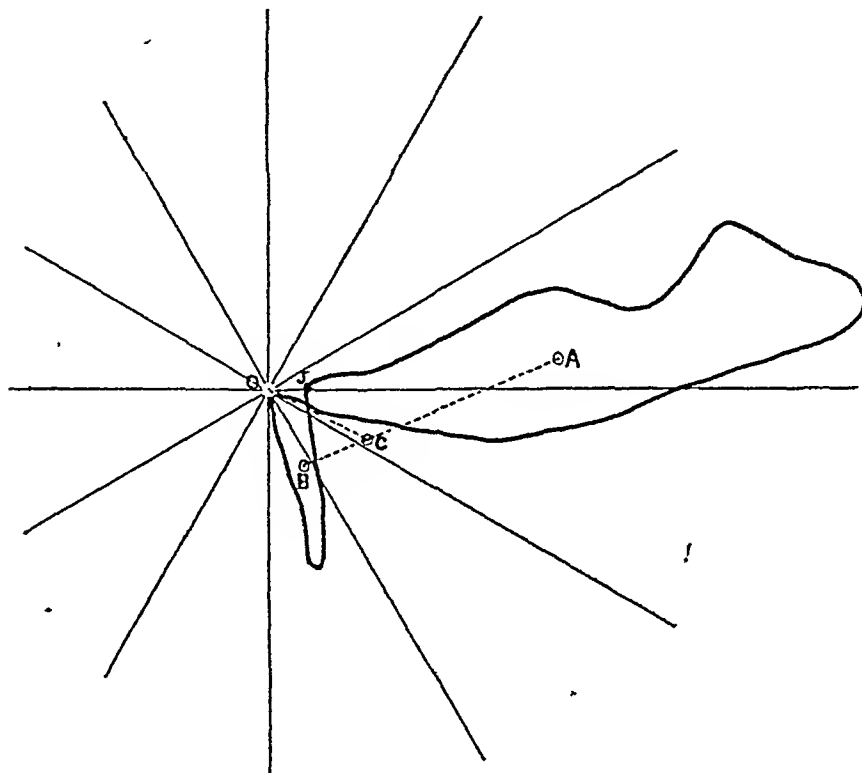


Fig. 7.—Calculation of the common center of gravity of QRS and T loops. The diagram represents a hypothetical case. The estimated center of gravity of QRS is at A, and that of T is at B. The assumed duration of QRS is 0.10 second, that of T is 0.30 second, and that of QRS-T is 0.40 second. The center of gravity of QRS-T is at some point O on the line AB. To locate O the calculation is as follows: $AO \times 0.10 \text{ (second)} = OB \times 0.30 \text{ (second)}$; $AO = 3 \text{ } OB$; $AO = 3 \text{ } (AB - AO) = \frac{3}{4} AB$; AB measures 5.8 cm., therefore $AO = 4.35 \text{ cm.}$ O being the center of gravity the line OC is the mean vector of QRS-T. The length of OC is 2.3 centimeters. Since 1 cm. represents $100 \mu\text{v}$, the magnitude of the mean vector, or of the potential gradient, is $230 \mu\text{v}$, and the time-potential gradient (Wilson's gradient) is $230 \times 0.4 \text{ second}$ or $92 \mu\text{v per second}$. The direction of the gradient is 26° .

THE RELATION OF THE VENTRICULAR GRADIENT TO THE VECTORCARDIOGRAM

Wilson and his co-workers^{12, 13} derived the concept of the ventricular gradient directly from the electrocardiogram but it also is possible to define the gradient in its relation to the VC. A brief statement of this relation will be made here. Some may find the concept more readily grasped if it is stated graphically in VC terms. Moreover, the argument will show that a rough approximation to the gradient may be made by mere inspection of the VC, and it is possible that such an estimate, although crude, may be of use in the practical application of gradient data in clinical medicine.

The ventricular gradient, as Wilson described it, is a vector having the direction of the mean electrical axis of the QRS-T period and a magnitude equal to the product of the mean manifest potential by the duration of the QRS-T

period. It is evident then that the magnitude of the ventricular gradient is a quantity having the dimensions of both voltage and time. This product is equal to the *manifest area* of QRS-T. It will be shown in the present discussion that it is possible to determine, directly from the VC, a vector having the direction of the mean electrical axis and a magnitude equal to the mean manifest potential unmodified by a time factor. This vector magnitude has only the dimension of voltage. It will be convenient for the purposes of this discussion to call the vector derived from the VC the *potential gradient* and to refer to the gradient calculated as described by Wilson as the *potential-time gradient*. Obviously the latter may be derived from the former by multiplying by the time duration of the QRS-T.

The following symbols with the stated meaning will be used in what follows.

E_m , a vector having the magnitude of the manifest potential and the direction given by the Einthoven equation, $e = E_m \cos \alpha$. The symbol sometimes may be interpreted as a magnitude without reference to direction.

\bar{E}_m , the mean vector of the infinite series of vectors, each equal to E_m throughout an interval (QRS, T, or QRS-T).

t , the duration of a time interval.

The possibility of deriving the potential gradient from the VC depends on the identity of the manifest potential, E_m , of the electrocardiogram and the generating vector of the VC, and the consequent identity of the mean vector, \bar{E}_m , for both curves. Since this matter is not one to *sauter aux yeux* a brief explanation may be helpful.

If it were technically possible to record the manifest potential differences (magnitude of E_m) instead of merely the components thereof, the tracing produced might appropriately be called the *manifest QRS-T*. The area under this curve would be the *manifest area* of QRS-T.⁶ The manifest QRS-T may be thought of as traced by the upper end of a vertical line, or ordinate, standing on the base line, representing by its length the varying magnitude of the manifest potential, E_m , and advancing at a constant rate by short equal steps, of length Δt . The mean ordinate of this curve obviously is the mean value of the manifest potential, that is, \bar{E}_m .

Turning now to the VC, we may picture it as traced by the terminus of a line which, like the ordinate of the manifest QRS-T, is equal in length to the manifest potential at every instant throughout the QRS-T period. But, unlike the vertical, evenly progressing, ordinate of the manifest QRS-T, the foot of the VC vector is fixed at the origin while the terminus sweeps through the field describing an arc to form a complete loop.

Both the vector of the VC and the ordinate of the manifest QRS-T represent the same electrical quantity, the manifest potential. They are essentially identical, except that the VC vector has direction as well as magnitude, whereas the ordinate has magnitude only, the varying direction of the electric force of which it is an expression being implicit in the ratio of the component voltages in two leads.

The analytical expression for the *mean manifest potential* is

$$\bar{E}_m = \frac{1}{t} \int_0^t E_m dt \quad (11)$$

This equation serves equally well to express the mean magnitude both of the ordinate of the manifest QRS-T and of the vector of the VC. The meaning of the equation, as it applies to the manifest QRS-T, may be clearer if it is pointed out that the integral, without division by time, is the magnitude of the area under the manifest QRS-T, that is the *manifest area*. If this manifest area is represented by an equivalent rectangle constructed on the base line under the manifest QRS-T it is evident that the height of the rectangle will be equal to the mean ordinate of the curve. The height of the rectangle is found by dividing the area by the length of the base, that is by the time. It is for this reason that the integral (manifest area) in the above equation is divided by t to give the value of the mean ordinate \bar{E}_m .

The application of the equation to the case of the VC is not quite so evident, since time is not shown explicitly in the VC. It therefore is desirable to replace dt by an element of arc, ds , provided the relation of ds to dt is known. This relation and the consequences of the substitution will be shown in what follows.

It at first will be assumed that the velocity of inscription of the VC is constant. The assumption does not greatly exceed the possibility, for an electrocardiogram in which the up and down strokes of QRS are approximately straight lines and form symmetrical peaks in both leads yields a QRS loop in which the velocity is nearly constant. If the velocity is constant then equal lengths of arc represent equal time intervals and the differential ds , representing an element of arc, may be substituted for dt , a corresponding change being made in the limits of integration and in the coefficient. When these substitutions are made Equation 11 becomes

$$\bar{E}_m = \frac{1}{s} \int_0^s E_m ds \quad (12)$$

The co-ordinates of the terminus of the mean vector \bar{E}_m , are given by the equations

$$\bar{x} = \frac{1}{s} \int_0^s x ds \quad \text{and} \quad \bar{y} = \frac{1}{s} \int_0^s y ds$$

These latter are the familiar equations for the centroid of a curve. Thus, the mean vector of a VC loop, if the latter is inscribed with constant velocity, can be constructed by drawing a straight line from the origin to the centroid of the loop.

The assumption of constant velocity now will be dropped and the influence of variable velocity examined. If a segment of the VC is slowly inscribed the vectors to that segment, spaced at equal time intervals, will be numerous and will "weight" the mean value of the vectors. Where the vectors are close set the amount of time in a unit length of the VC will be large. In the VC, time

may be considered as analogous to mass in the case of a thin wire formed in a loop, and it has the same effect on the center of gravity, i.e., slowness of inscription in one segment will cause a displacement of the center of gravity toward the segment. Carrying the analogy further and remembering that the density of a wire is the mass per unit length, we may coin the expression *time density* for use with the VC, and define the term as the amount of time in a unit length of the VC. If ρ represents time density, $\rho = \frac{dt}{ds}$ or $dt = \rho ds$. Evidently ρ is the reciprocal of the velocity.

If, now, the differential, dt in Equation 11, is replaced by ρds , we obtain the equation for the mean vector of a VC of variable velocity.

$$\bar{E}_m = \frac{\int_0^s \rho E_m ds}{\int_0^s \rho ds} \quad (13)$$

Corresponding equations for the co-ordinates of the terminus of the mean vector readily may be written, and these will be also the equations for the co-ordinates of the center of gravity of the loop. It is apparent then that the terminus of the mean vector of a VC loop is at the center of gravity of the loop, whether the velocity of inscription is constant or variable.

With these relations in mind, a rule now may be formulated for an approximate method of locating the center of gravity of a VC loop and thereby determining the mean vector, or the potential gradient. By inspection locate and mark the center of gravity of the loop considered as if it were of uniform time density, allowing due weight for the large moment of portions of an irregular curve that project far out from the general region included by the curve, and for the lesser moment of re-entrant portions of the curve. Then roughly estimate the relative velocity in the several parts of the curve, using the velocity equation (Equation 10) mentally applied. Crosshatch the curve with close set lines to indicate slow inscription and with widely spaced lines in regions of high velocity. The cross hatching serves to indicate the estimated variations in the time density. Then choose a point removed from the geometrical centroid in a direction and for a distance which allows for the "weight" of regions of slow velocity and for the "lightness" of regions of high velocity. The center of gravity is shifted toward "heavy" regions, away from "lighter" regions. But it should be remembered that the principle of the lever is involved in center of gravity dynamics; consequently the influence of weight of segment varies with the distance from the center of gravity. A more exact statement of the dynamic principles involved is given in an appendix.*

*The reader readily may test his ability to make fair estimates of the center of gravity of VC loops in the following way. Shape a piece of copper wire to form an irregular loop in one plane. Draw the outline of this loop on paper and mark a point which is estimated to be at the center of gravity. Now slip a thread, held taut, under the wire and move the thread until, when it is lifted slightly, the loop is found to be in balance. Mark the position of the thread and draw a line to show the position. Repeat this operation with the thread crossing the loop at a considerable angle from its first direction. Draw a line to show this second balance position of the thread. The intersection of the two lines is at the center of gravity of the loop. This test, when made by a number of people, revealed a considerable innate capacity for making a good estimate.

Having located the center of gravity of both the QRS and the T loops, the center of gravity of the whole VC is to be found. Here, again, time plays the role of mass. The duration, or mass, of QRS and that of T may be considered as concentrated at the respective centers of gravity of the loops. The common center of gravity (Fig. 7) lies on a connecting line AB at a point C that subdivides AB according to the equality of moment arms principle, that is, so that

$$Mass_A \times AC = Mass_B \times CB$$

For practical use this equation may be transformed to give AC in terms of quantities readily measured on the electrocardiogram and VC. Thus we have

$$AC = \frac{T \text{ interval}}{QRS-T \text{ interval}} \times AB$$

A line drawn from the center of the field to the point C is the mean vector of the whole ventricular complex, or the potential gradient. It may be measured by means of a scale to give the magnitude of the gradient and, by means of a protractor, for the direction.

Those who have taken the pains needed to make accurate determinations of ventricular gradients by Wilson's method of area measurements on the electrocardiogram may be skeptical of the reliability of gradient estimates based on intuitive judgments of this sort but, on trial, results were obtained which suggest that the method may be useful for some purposes. These results are illustrated in Fig. 8 and tabulated in Table I.

TABLE I. THE POTENTIAL-TIME GRADIENT DETERMINED FROM ESTIMATE OF THE CENTROID OF THE QRS LOOP OF THE CONSTRUCTED VC AND COMPARED WITH THE SAME FUNCTION DETERMINED BY WILSON'S METHOD OF AREA MEASUREMENTS

CASE	FROM ESTIMATE OF CENTROID OF QRS LOOP OF VC		FROM AREA MEASUREMENTS OF QRS IN ELECTROCARDIOGRAM	
	MAGNITUDE IN $\mu\text{V/SEC.}$	ANGLE	MAGNITUDE IN $\mu\text{V/SEC.}$	ANGLE
1	84	- 41°	84	- 36°
2	174	- 56°	186	- 64°
3	164	- 44°	140	- 52°
4	25	- 42°	42	- 33°
5	92	-172°	83	-147°
6	70	- 83°	68	- 83°

For graphic representation of these quantities see Fig. 8.

The electrocardiograms and the recorded VC's are reproduced from records of six cases published by Wilson and Johnston,¹ who kindly furnished me with photographic copies of the records. The constructed VC's were drawn from the electrocardiograms without the recorded VC's being in view or in mind. Drawn several years ago at the beginning of these studies they represent the approximations to the true VC which may be made by a novice. The gradient determinations were made recently and without any previous experience in estimating this function. In this test only the QRS period was dealt with; presumably the results would have been about as good if the whole QRS-T period had been covered.

The units in which the magnitude of the voltage gradient is expressed may be chosen at will, but the microvolt, used by Wilson, is well suited for the measurement of the mean vector as derived from the VC. The field described

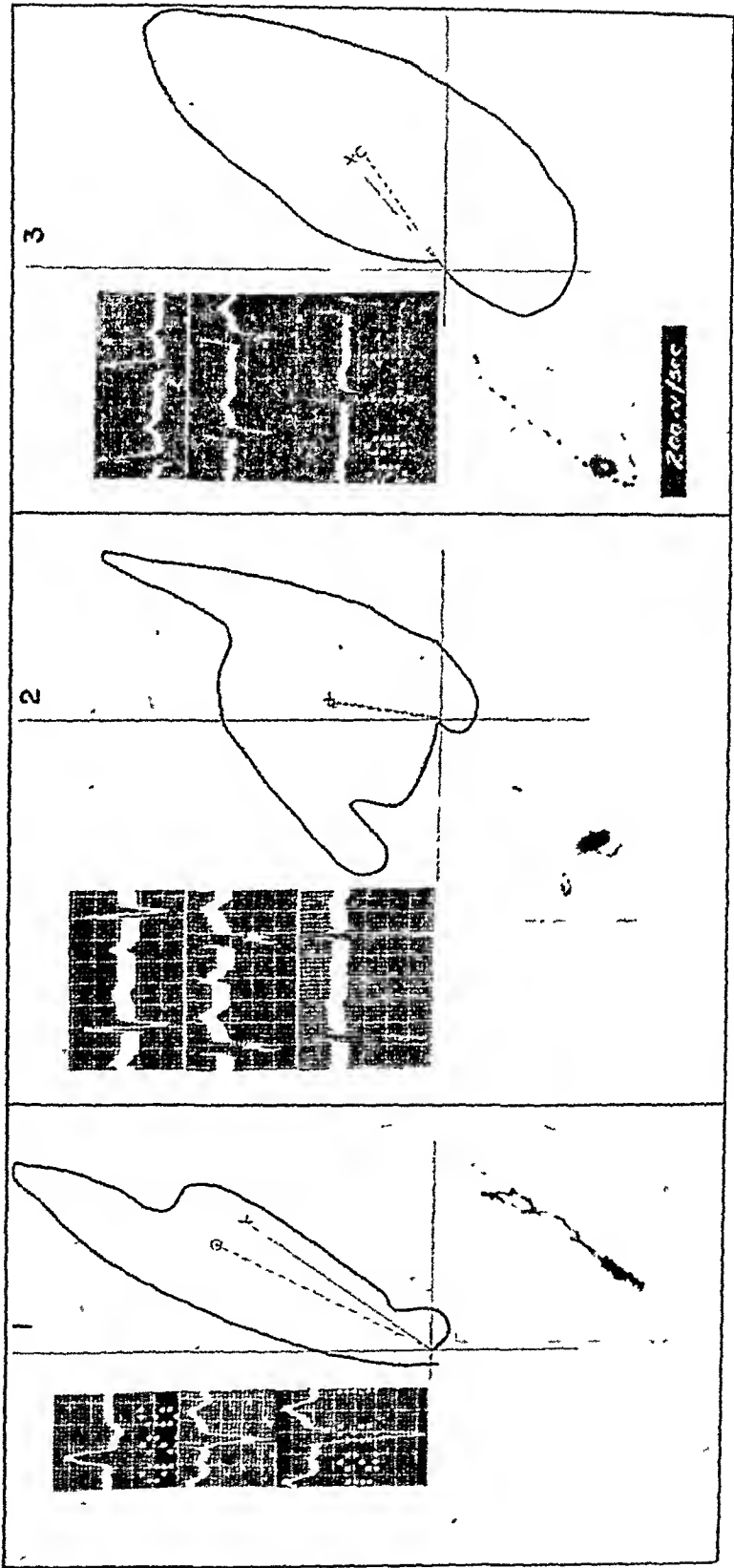
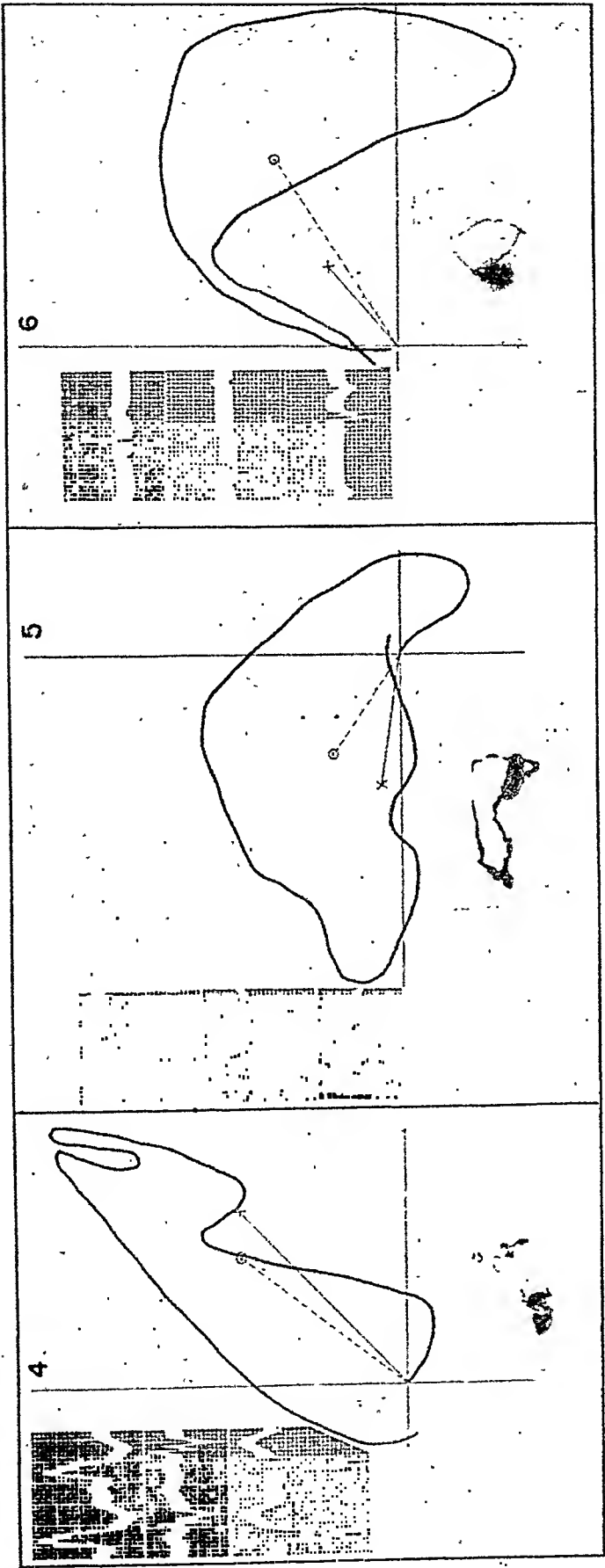


Fig. 8.—Upper half. (For legend see opposite page.)



Lower half.

Fig. 8.—Constructed VC's of six cases are shown, with the electrocardiograms and the VC's recorded by Wilson. In each constructed VC the estimated mean vector is shown as a broken line from the origin to a point marked by a small circle. The mean vector determined by the method of measured areas is shown as a continuous line ending in a small x. The estimation of the mean vector in the VC's in the lower row is less satisfactory, the errors being due chiefly to avoidable faults in sketching the VC or in estimating the relative velocity of inscription in certain segments. Some of these faults are obvious and may be more instructive than if the execution were faultless. For numerical data see Table I.

early in this paper is so constructed that 1 cm. along any radius represents 0.1 mv or 100 μ v potential difference in that direction. If it is desired to transform the magnitude of the potential gradient to a quantity identical with the potential-time gradient of Wilson it is necessary only to multiply the magnitude of the potential gradient by the duration of the QRS-T interval expressed as a fraction of a second.

CONCLUSIONS

The vectorcardiogram is of value, first of all, because it exhibits the behavior of the heart's electric vector simply and realistically. Wilson and Johnston¹ in their paper on the recorded vectorcardiogram, observed that, for teaching purposes, "It makes it possible to visualize the electromotive force of the heart as a single natural entity unobscured by the artificialities and complexities introduced by splitting it into a system of components in the arbitrary frame of reference defined by the standard leads." But if the unitary and simple character of the VC aids the beginner to grasp more clearly the course of electrical events in the heart it is not, perhaps, extravagant to say that all who attempt interpretation of the electrocardiogram likewise would derive from the VC clearer views of the electrical events and thus might more surely arrive at true meanings. Electrocardiography has become cluttered by a mass of detail, a consequence of dealing with a threefold complex of components instead of the single entity expressed by the components. The remedy for this particularism is the recognition of elementary characteristics of vector behavior and a diligent study of correlations between these prime features and known cardiac processes and states. The grammar of the electrocardiogram cannot yet be written, but to illustrate the thought expressed here several basic characteristics of the VC may be mentioned—the magnitude and the direction of the major axes of the two VC loops, the angle of divergence of the two loops, the direction of rotation, the ratio of the major and minor axes of the loops, and the direction and amount of displacement of *J*. In addition there should be mentioned the ventricular gradient, the early studies of which already give promise of utility. If electrocardiography is to progress and if it is to be intelligible to those whose varied interests preclude specialization, then it seems to be imperative that the threefold Einthoven record be integrated to make possible clear concepts and simple descriptions.

In a later paper I hope to report on a study now in progress on the basis of which a number of electrocardiographic patterns will be discussed in the light of the VC representation. However, one of the observations already made may be stated here to illustrate how the VC possibly may extend the range of information derived from the electrocardiogram. On examining the sense of rotation of the QRS loop in the records of about fifty presumably normal individuals a positive (clockwise) rotation was found in all but two or three. Moreover the rotation of T also was found to be positive. On the other hand, in a group of cases with left axis deviation, but without other evidence of abnormality, the rotation of the QRS loop was negative. In these the rotation of T also was negative. But in still another group showing left axis deviation, together with well-marked clinical evidence of myocardial disease, the rotation of the QRS loop was positive, while that of T was negative. These observations are

not yet extensive enough, nor made in sufficient detail, to warrant a firm conclusion, but it seems likely that, when the heart is normal and in the average normal position in the chest, the rotation of the QRS loop always is positive, with positive rotation of T; that, as left axis deviation develops, the inclination of the plane of the spatial vector motion changes so that, in the frontal plane, the rotation of QRS appears negative; but that, if the myocardium then becomes seriously diseased, the rotation of the leftwardly deviated QRS loop is reversed, becoming positive again, while the rotation of T remains negative and opposed to that of QRS. If further studies confirm this apparent influence of myocardial disease on the sense of rotation of the loops and on the concordance of rotation in the two loops, then the VC representation can be said to have revealed a sign of disease which is implicit, but not apparent, in the electrocardiogram.

In Aristotelian metaphysics it was taught that the result of a synthesis is a new entity, not merely the sum of the parts. The truth of this aphorism is exemplified in many fields of science. Appositely, the VC may be viewed as an entity having a capacity for usefulness beyond that of the electrocardiogram from which it is derived. The technique of VC construction described in this paper provides a means by which the worker in electrocardiography readily may explore this possibility without the need of apparatus of any sort.

APPENDIX

The Center of Gravity of a Loop of Varied Velocity.—As stated earlier in this paper, it is possible to make a fair estimate of the approximate position of the center of gravity of the VC by mere inspection of the curve. But a judgment of this sort is more likely to be good if there is understanding of the dynamic principles involved. The following analysis of a simplified, but pertinent, center of gravity problem should be helpful to such an understanding. But the method used, although exact in principle, scarcely can be applied exactly to an actual VC. The problem and its solution are presented merely as an aid to intuitive judgment.

The half cardioid *ODEF* (Fig. 9) and the half loop of a "four leaf rose" *FGO* are joined to represent an asymmetrical QRS loop. For measurements, the intercept on the x axis is taken as unity. The centroid of *ODEF* is at A ($\bar{x} = 0.4$, $\bar{y} = 0.4$), that of *FGO* is at B ($\bar{x} = 0.518$, $\bar{y} = -0.175$). The ratio of the length of *ODEF* to that of *FGO* is 2:1.25. Assuming that a line has density and that the loop is of uniform density the masses of the two curves are respectively proportional to their lengths. Indicating the mass of the cardioid portion of the loop by M_c and that of the rose portion by M_r we have

$$\frac{M_r}{M_c} = \frac{1.25}{2.00}$$

For the purpose of dynamic analysis the whole mass of a line may be considered as concentrated at its centroid. Hence the center of gravity C of the loop is identical with the center of gravity of the two masses concentrated at A and at B , respectively. The location of C is to be found by employing the principle of equality of moment arms. Thus

$$M_c \times AC = M_r \times CB \text{ or } \frac{AC}{CB} = \frac{M_r}{M_c} = \frac{1.25}{2.00}$$

If the velocity in one segment of the loop is varied the center of gravity will be displaced, provided the concept of "time density" (time per unit of length) is substituted for the usual concept of density (mass per unit of length). The time density is the reciprocal of the velocity and will be represented by ρ . If the time density in a segment is increased, the center of gravity will be displaced toward this segment; a decrease in the time density will cause a displacement in the opposite direction.

To define this effect more exactly the loop now will be supposed to have uniform velocity except in the segment to the left of the y axis, where a different, but uniform, velocity obtains. P is the center of gravity of this segment, with co-ordinates, $\bar{x} = -0.83$, $\bar{y} = 0.242$. It is desired to calculate the displacement of the center of gravity from the point C caused by the variation of time density in the segment. If the time density in the varied segment is n times the unit density prevailing in the rest of the loop the variation of time density will be $n\rho - \rho$

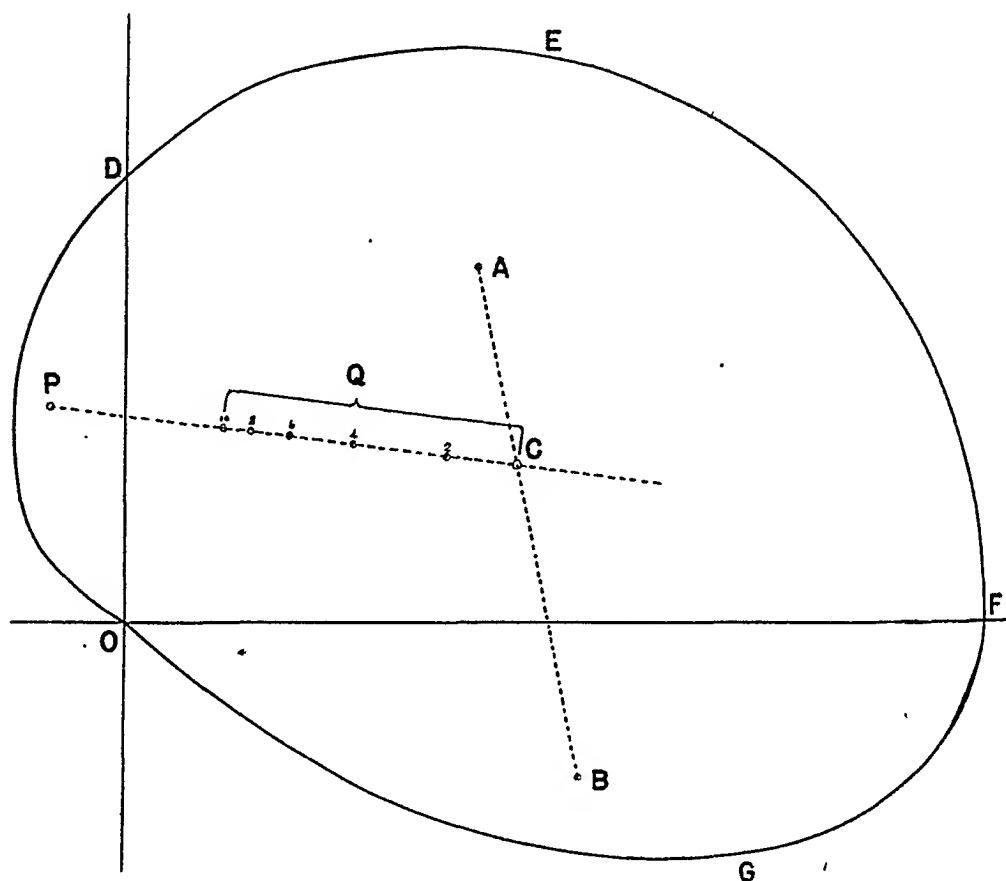


Fig. 9.—Conventionalized QRS loop formed by joining the half cardioid $ODEF$ ($Qr = \cos \theta + 1$), to half of one leaf of a "four leaf rose" FGO ($r = \cos 2\theta$). The intercept on the x axis is taken as unity. Length of half cardioid = 2; length of half rose leaf = 1.25; length of segment to left of y axis = 0.586; A is at centroid of half cardioid ($x = 0.4$, $y = 0.4$); B is at centroid of half rose leaf ($x = 0.518$, $y = -0.175$); C is at centroid of combined curve ($x = 0.446$, $y = 0.179$); P is at centroid of segment to left of y axis ($x = -0.83$, $y = 0.242$); Q indicates variable location of center of gravity of the whole loop dependent on the "time density" of the segment to left of the y axis; numerals indicate the respective locations of the center of gravity of the whole loop, with the time density varying from 1 to 10.

or $(n - 1)\rho$. The variation of mass of the segment is given by the product of the time density by the length (l) of the segment, that is, it is $(n - 1)\rho l$. If this amount of mass is considered to be concentrated at P , the centroid of the segment, while the mass of the whole loop of uniform density is concentrated at C , then the new center of gravity Q may be found by application of the principle of equality of moment arms. If the mass of the whole loop of uniform time density is expressed by ρL (where L is the whole length of the loop) then we may write the equation

$$CQ \times \rho L = QP \times (n - 1)\rho l$$

$$\text{or } \frac{CQ}{QP} = \frac{(n - 1)\rho l}{\rho L}$$

If the length l of the segment is expressed as a fraction of the total length, L , of the loop, the last equation may be written

$$\frac{CQ}{CP} = \frac{(n-1)l}{(n-1)l+1}$$

The idea expressed by this last equation may be shown in another and simpler form if the symbol ΔM_s is used for the variation of mass of the segment. Thus percentage displacement

$$\text{of } Q \text{ toward } P = \frac{\Delta M_s}{\Delta M_s + 1} \quad (14)$$

If the velocity of inscription in the varied segment is greater than in the rest of the loop n is negative and the displacement of the center of gravity is to be measured on the extension of PC away from the segment.

Returning to the diagram of Fig. 8 we may, by way of illustration, calculate the displacement of the center of gravity on the assumption that the velocity of inscription of the segment is one-fourth as great as in the rest of the loop. In this case the time density is fourfold and $n = 4$. The variation of density, $n - 1$, is 3. The length of the whole loop is 3.25, while that of the segment is 0.59, making the relative length of the segment 0.18. Thus the variation of mass, $(n - 1)l$, is 0.54. Then by Equation 14 we have

$$\frac{CQ}{CP} = \frac{0.54}{1.54} = 0.35$$

We conclude that the fourfold slowing of inscription of the segment causes displacement of the center of gravity from its position at C to a point, Q , about one-third of the distance toward P .

In the diagram the points along the line, CP , represent the several positions of the center of gravity when the time density of the segment has the several values shown by the adjacent numerals.

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DIFFERENCES IN BLOOD PRESSURE VALUES DETERMINED BY INFLATING AND DEFLATING THE CUFF OF THE- SPHYGMOMANOMETER

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IF ONE listens carefully for arterial tones, a different set of blood pressure readings will be found while the sphygmomanometer cuff is being inflated than will be found when the cuff is being deflated. Both maneuvers were employed in 200 out of 3,000 recent examinations, and the findings were recorded. The majority of the patients examined were white men of average height and weight between the ages of 20 and 50 years. They were chiefly ex-military personnel who were referred for routine examinations.

The procedure consisted of a period of thirty to sixty minutes' rest during which the history was taken. The patient was stripped for measurement of the height and weight and for inspection for scars and defects. He remained seated for examination of the eyes, ears, nose, and throat. He moved eight feet to another stool for determination of the temperature, the pulse rate, respiratory rate, and the blood pressure, and for examination of the heart and lungs. Thus, a sufficient period of rest following light activity was routine.

In making measurements of the blood pressure care was observed in placing the sphygmomanometer cuff on the left arm smoothly and in such a way that pressure would not force the lower edge of the cuff against the stethoscope, so that noise would not be produced. The cuff was inflated slowly until the first sound (diastolic reading) was audible. It was then inflated more rapidly, but smoothly, until the sounds disappeared (systolic reading). After raising the mercury column 30 to 40 mm. higher, the pressure was then determined in the usual manner with the mercury falling. Thus, the first sound to appear when the cuff was inflated corresponded to the last sound when it was deflated, and the last sound during inflation corresponded to the first sound on deflation.

In the second phase of inflation the mercury column was raised at a rate of 4 to 6 mm. per heartbeat. This permitted an error of 5 mm. in the readings. This may be considered as an objection to the test, but this error, as shown in Table I, is no more than a +6 mm. in the difference column and does not explain the minus differences that are found in those cases showing a lower systolic pressure by the standard method; nor does it explain the plus differences of 20 mm. or more. This error is unavoidable as some possible reflex mechanism is given time to exert its balancing influence if the rate of inflation is too slow. Thus, a bradycardia extends the error to the point of nullifying the test. No such error, however, occurs in the diastolic readings. While experimenting with

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TABLE I.

TYPE	ESVD	PATIENT	DIAGNOSIS	A	B	DIFFERENCE
1	3	FLS	Hypertension	160	206	+46
				118	110	-8
2	18	JS	Arteriosclerosis	118	128	+10
				74	82	+8
3	8	JBB	Hypertension	210	220	+10
				130	130	0
4	176	HA	Trauma	120	120	0
				80	82	+2
5	44	FJS	Valvular heart disease	110	110	0
				86	84	-2
6	37	GHH	Pericarditis	118	118	0
				74	74	0
7	106	SM	Muscular atrophy	154	150	-4
				92	92	0
8	41	NON	Valvular heart disease	106	94	-12
				76	64	-12
9	79	FHW	Neurasthenia	100	94	-6
				66	70	+4

A = Readings taken during inflation of the sphygmomanometer cuff.

B = Readings taken during deflation of the sphygmomanometer cuff.

this test in some cases of hypertension it was observed that the systolic peak seemed to follow the cuff pressure. That is, the sounds might disappear at a certain level during inflation of the cuff, only to return if the inflation were stopped at that level; the sounds might disappear on further inflation and re-appear at a higher level until a maximum point was reached beyond which there was no further rise.

In the standard method the disappearance of sound was recorded as the diastolic reading. An interesting observation was the fact that, in most cases, the cuff pressure could be left for thirty seconds or more immediately below the first diastolic reading and no sound could be heard even though the diastolic level by the standard method was below the first reading. For example, as the mercury was rising the first sound came in at 82 mm. and as it was falling the last sound was heard at 78 mm., but a repetition of the procedure and maintenance of the cuff pressure at 80 mm. for about ten seconds did not elicit a sound. It was noted that when there was a difference between the change of sound and the disappearance of sound during deflation, the diastolic reading during inflation more nearly corresponded to the change of sound. From this it is believed that the change of sound marks the true diastolic pressure and the sound produced with less cuff pressure is caused by vascular dilatation. This may be a compensation for an increased systolic pressure caused by a reflex stimulation arising from the pressure on the arteries in the arm during the sphygmomanometry. That such a reaction occurs is denied by Hamilton and his co-workers¹ who measured the intra-arterial pressure with a needle in the artery and compared it with sphygmomanometer measurements taken simultaneously in the other arm. He reported that the two methods gave reasonably identical results. It is possible, however, that a needle in an artery establishes the same sort of sensory stimulus as pressure on the artery by a sphygmo-

nometer cuff. Kotte and his associates² wrote, "The only pain which the subjects noted was felt as a brief twinge at the moment of arterial puncture." At least the intra-arterial method is not stimulus-free and it is possible that every known method of measuring blood pressure affects the tension by its mere application.

In this series of approximately 3,000 patients only 200 were suitable for study for the same reasons given by numerous investigators³⁻⁸ as sources of error in sphygmomanometry, namely: excessive obesity or emaciation, weak Korotkow sounds, high noise level of the room, noisy inflating mechanism, and involuntary tremors of the subject. Some subjects were rejected because the procedure of examination deviated from the routine, time was at a premium, or the pulse was too slow.

In this series nine types of response to the pressure of the sphygmomanometer cuff were noted consisting of no change, a rise, or a fall in the systolic and/or diastolic pressures. An example of each type is shown in Table I. Of the first type (in which the systolic pressure was higher and the diastolic lower by the deflation than by the inflation method) there were 109 cases (54.5 per cent); of the second type, 53 (26.5 per cent); the third, 12 (6 per cent); the fourth, one (0.5 per cent); the fifth, two (1 per cent); the sixth, three (1.5 per cent); the seventh, one (0.5 per cent); the eighth, 15 (7.5 per cent); and the ninth, four (2 per cent). In the first group the greatest differences were noted, chiefly from cases of hypertension. All of the hypertensive conditions fell in Groups 1, 2, or 3.

SUMMARY AND CONCLUSIONS

A method of measuring the blood pressure for comparison with the standard procedure is described. Compression by the sphygmomanometer cuff appears to produce a change in the blood pressure so that the systolic reading usually is higher and the diastolic lower after the cuff is inflated. It is suggested that this apparent response is the result of a stimulus from the vascular autonomic system reflexly affecting the cardiac and vascular tone and that the type and degree of response depends upon which fibers are hyperirritable at the time.

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Clinical Reports

METASTATIC CARCINOMA AS A CAUSE OF CONSTRICTIVE PERICARDITIS

REPORT OF A CASE

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REPORTS of metastatic tumors of the pericardium producing chronic cardiac compression with secondary right-sided heart failure are quite rare. The following case of primary bronchogenic carcinoma with metastasis to the pericardium is an example of such a case.

CASE REPORT

A Negro man, 41 years of age, was admitted to an Army general hospital on Aug. 24, 1943. The past personal and family history were not significant. In May, 1943, the patient gradually developed shortness of breath on exertion, moderate pain in the substernal region and near the right shoulder blade, occasional productive cough with expectoration of clear mucoid sputum, night sweats, and anorexia, and lost 30 pounds in weight. Because of the persistence of these symptoms, the patient reported to the dispensary and was admitted to the station hospital. Examination at that time revealed enlarged lymph glands in the cervical and supraclavicular regions, impaired resonance over the right upper anterior chest and mediastinum and moist râles throughout the chest. There was x-ray evidence of enlargement of the superior mediastinum and biopsy of a cervical lymph node was reported to show hyperplastic lymphadenitis. He was transferred to an Army general hospital.

Examination at the time of admission revealed a chronically ill, emaciated patient with evidence of enlargement of the superior mediastinum and moderate clubbing of the fingers and toes. During the first part of his hospital stay, his course was essentially uneventful, except for a troublesome "brassy" cough and an occasional slight hemoptysis. A biopsy of a right axillary node was reported as reactive lymphadenitis, but, upon review by another source, was thought to represent an early stage of Boeck's sarcoid.

Repeated urinalyses were essentially normal, and several blood counts revealed a mild secondary anemia with a leucocyte count ranging from 6,000 to 11,000, with a normal differential. The sedimentation rate was persistently elevated to 60 mm. in one hour. Seven sputum examinations were negative for tubercle bacilli. The Kahn reaction on the blood and spinal fluid was negative. The total protein of the blood serum was 5.9 Gm. per 100 c.c., with an albumin-globulin ratio of 1:1.3. Values for serum calcium, phosphorus, and phosphatase were normal. A biopsy of the bone marrow revealed atrophic marrow.

An x-ray of the chest in August, 1943, revealed a tumor mass involving the superior mediastinum with enlargement of adjacent lymph nodes. The cardiac silhouette was nor-

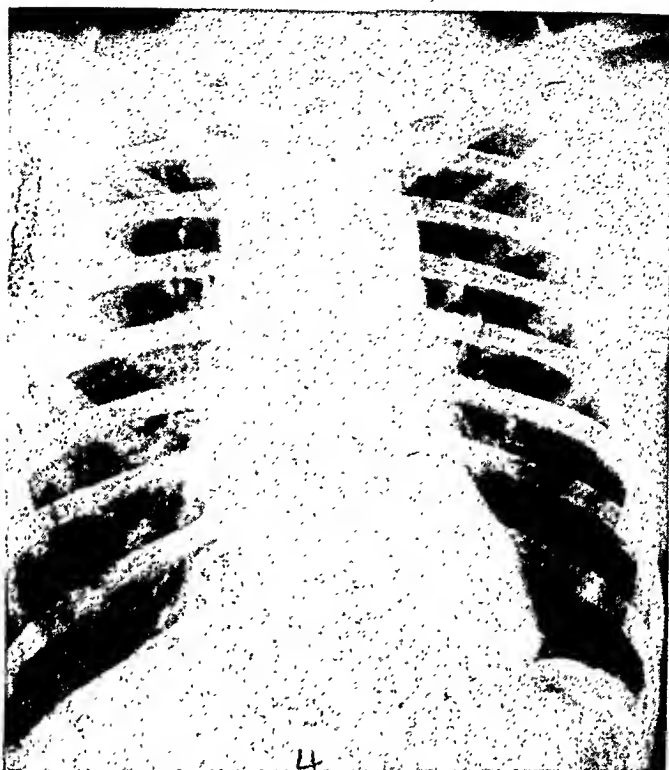


Fig. 1.—Film taken July 11, 1943, showing enlargement of the superior mediastinum and right hilar region.



Fig. 2.—Film taken on induction shows enlarged glands in the right hilum and right para-aortic area.

mal in size and shape. X-ray examination of the long bones and hands revealed hypertrophic pulmonary osteoarthropathy.

About five months after onset, in October, 1943, the patient developed a sharp precordial pain aggravated by movement and inspiration. A loud, to-and-fro, leathery friction rub was heard over the precordium. Serial electrocardiograms showed evidence of acute pericarditis, and, in addition, persistent low amplitude of the QRS complexes in all leads, suggesting tamponade or chronic pericarditis. The area of cardiac dullness increased markedly to the right and left. The apex impulse was palpated diffusely in the fifth intercostal space. The heart sounds were well heard and the first sound at the mitral area was accentuated.

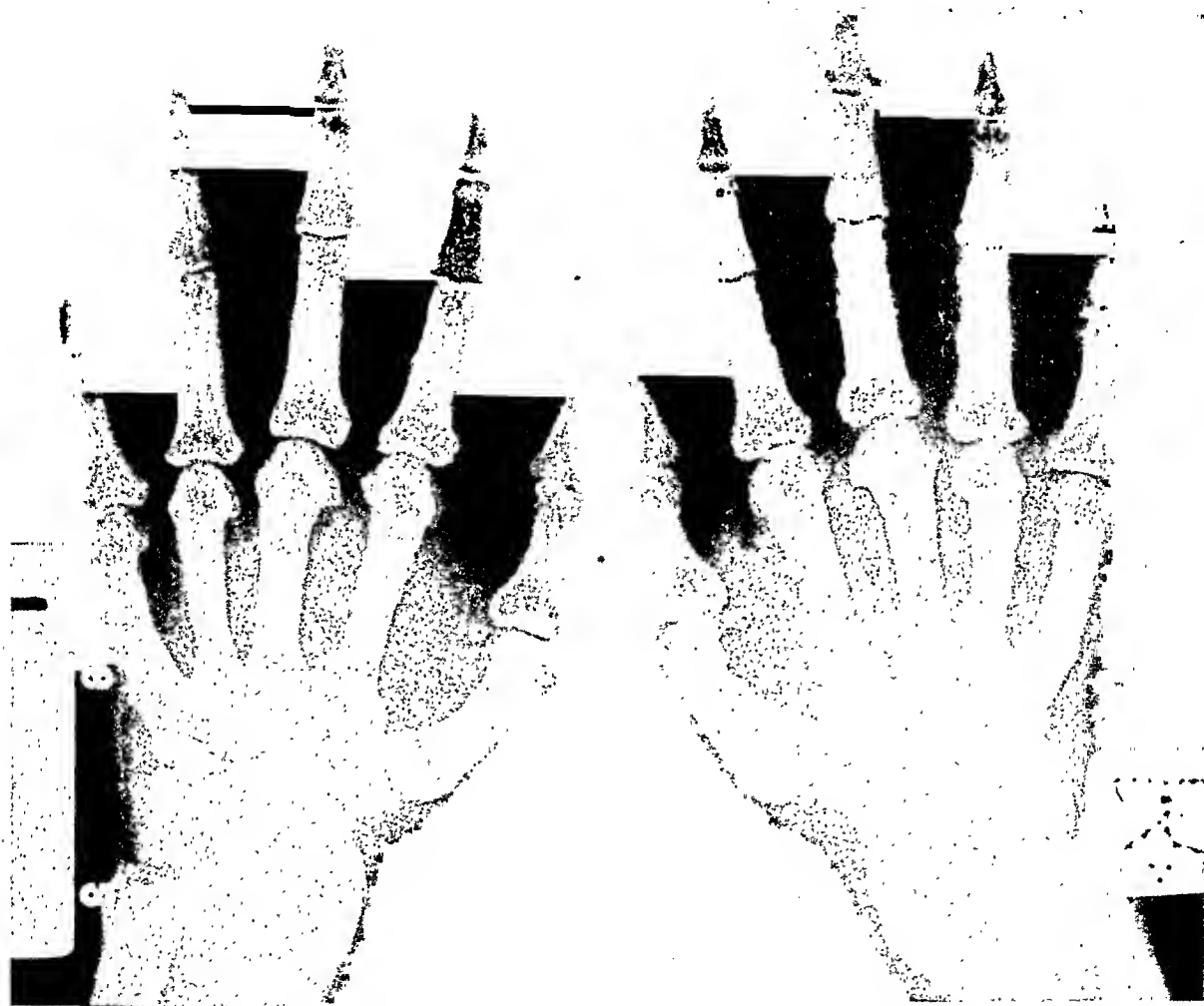


Fig. 3.—Films of hands showing hypertrophic pulmonary osteoarthropathy involving the shafts of the metacarpal bones.

The pulmonic second sound was not remarkable. The blood pressure measured 116/70. The neck veins were struttled in the recumbent position but were not distended in the upright position. The venous pressure was 150 mm. of saline. Fluoroscopy revealed marked enlargement of the cardiac silhouette, both to the right and to the left, diminished pulsations in the region of the left ventricle, and an irregularity along the left cardiac border suggesting a nodule in the pericardium. About one month after the onset of the pericarditis, there gradually developed a marked pitting edema of both legs, extending as high as the knees. The liver was palpable 3 fingerbreadths beneath the costal margin. The patient, during this period, had occasional episodes of dyspnea for which oxygen was given with relief, but during the greater portion of the time, he was able to lie flat in bed without difficulty. At one time, a small pleural effusion developed on the right side. It was

believed that the clinical features were those of right-sided heart failure. These symptoms gradually subsided and the further course was uneventful until Jan. 15, 1944, when he experienced increasing dyspnea. By physical examination and by x-ray films, taken in both inspiration and expiration, it was determined that he had an acute emphysema involving the entire right lung, due to a ball valve mechanism in the right main stem bronchus. His condition grew steadily more serious, and he expired on Feb. 23, 1944.

Neeropsy examination revealed an extensive bronchogenic carcinoma, primary in the right main stem bronchus, with obstructive emphysema of the right lung. The pericardium presented an extraordinary appearance. The visceral and parietal pericardium was edematous and adherent. There was extensive infiltration of the pericardium by firm, nodular,

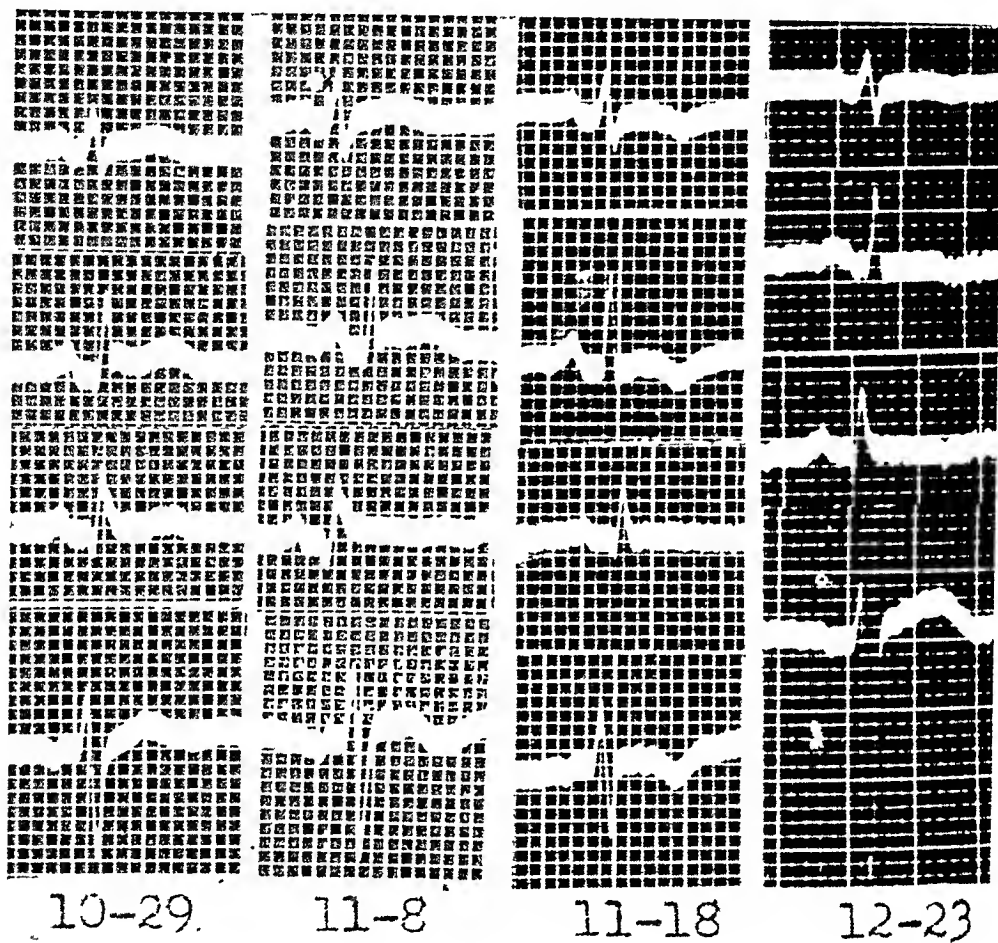


Fig. 4.—Note the serial electrocardiographic changes of acute pericarditis with the addition of low amplitude of all QRS complexes in the standard leads, and persistent inversion of the T waves suggesting chronic pericarditis.

gray, tumor tissue. This formed a mass, averaging 2.5 cm. in thickness, that completely encased the heart. The heart appeared to be normal in size and there was no hypertrophy of either ventricle. The myocardium was not invaded by tumor tissue. Microscopic examination revealed the primary and metastatic tumors to be composed of solid masses of polygonal cells with vesicular nuclei with moderate anaplasia and irregular mitoses. There was a suggestion of an acinar arrangement in some areas. The pathologic diagnosis was: (1) bronchogenic carcinoma, Grade 2, of the right main bronchus; (2) metastases to mediastinal lymph nodes, pericardium, and adrenal glands; (3) emphysema of the right lung; and (4) hypertrophic pulmonary osteoarthropathy.



Fig. 5.—Film taken Nov. 2, 1944, showing marked enlargement of cardiac silhouette to the left and enlargement of the superior mediastinum. Note enlarged glands in right hilar region.



Fig. 6.—Film taken Jan. 21, 1944, showing emphysema of right lung with widening of intercostal spaces and shifting of mediastinum to the left. Note the irregular cardiac shadow and superior mediastinal mass.



Fig. 7.—Note primary site of bronchogenic carcinoma in right main stem bronchus.

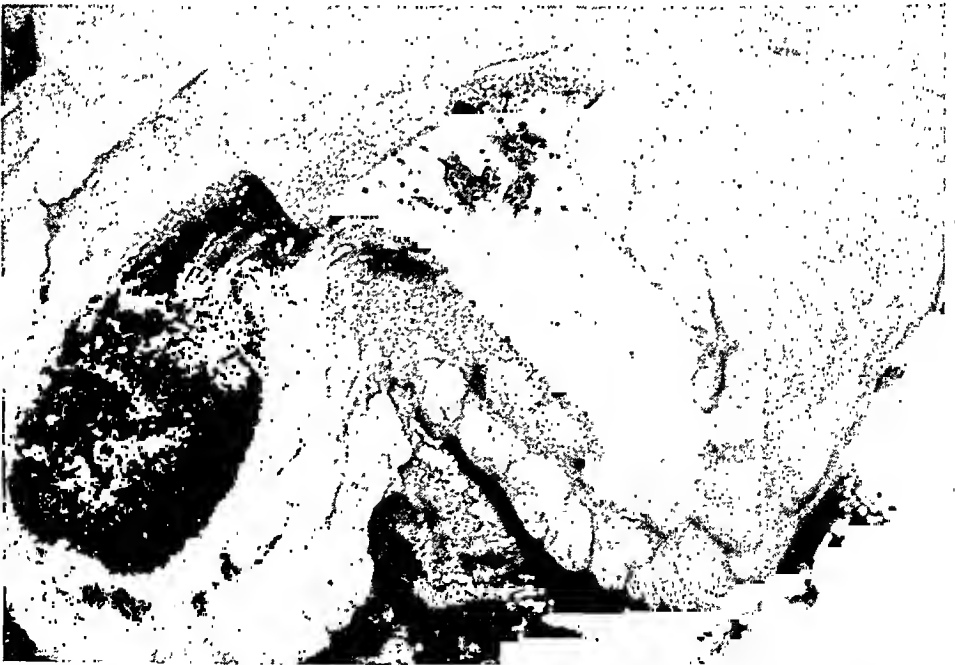


Fig. 8.—Note the dense growth of tumor in the pericardium about the heart which has been opened. The heart was of normal size and was not invaded by tumor tissue.

COMMENT

In view of the history and findings at the time of admission, bronchogenic carcinoma was thought to be present. Later, the diagnosis of sarcoid, as a result of a biopsy of an axillary gland, led to some confusion and it was thought that the clinical picture could be explained on this basis. The occurrence of acute pericarditis during the course of the illness was compatible with either disease entity. At the time of the occurrence of congestive heart failure, the clinical picture was that of right-sided heart failure. This was thought to be due to cardiac compression or to chronic cor pulmonale, secondary to pulmonary infiltration or extrinsic pressure on the pulmonary artery. Following fluoroscopy, it was thought that the most likely explanation was chronic compression of the heart by tumor tissue. The electrocardiographic changes were of interest, demonstrating the S-T segment changes of acute pericarditis as well as low amplitude of all QRS complexes, such as is seen in chronic pericarditis or in the presence of an effusion. The T waves subsequently became inverted in all leads, and these changes persisted. At no time was an arrhythmia, such as auricular fibrillation, noted. This was noted in 38 per cent of Harrison and White's series.¹

Reports of metastatic tumors of the pericardium are not uncommon; however, obliteration of the pericardial cavity by such a process is rare. The production of the syndrome of constrictive pericarditis is even more rare. Scott and Garvin² reported involvement of the pericardium by metastases in 61 of 1,082 cases of malignancy in 11,100 consecutive autopsies. The heart was involved in 79 instances, the heart and parietal pericardium together in 22, and the heart or parietal pericardium, or both, in 118. The bronchus and breast were the most common sites of primary tumor. In only one instance was the pericardial cavity obliterated. Seven cases showed myocardial insufficiency and none were reported to be due to cardiac compression. Yater³ reported 11 cases of neoplasm involving the pericardium and in no case was the pericardial cavity obliterated. Henninger⁴ reported four cases of metastasis to the pericardium, but none exhibited congestive cardiac failure. The parietal pericardium in Case 2 of his series was closely adherent to the epicardium. Langford and Thomas⁵ reported a case in which the pericardial cavity was obliterated by metastases from a hypernephroma, but cardiac failure was not present. Leaman⁶ reported a case of bronchogenic carcinoma with metastases to the heart, with obliteration of the pericardium, which completely encased the heart and produced cardiac failure. Beck⁷ reported two cases of chronic cardiac compression from invasion of the parietal pericardium and mediastinum by sarcoma. The pericardium was thickened, but not adherent to the heart. Thus, it is seen that neoplastic involvement of the pericardium may be a rare cause of constrictive pericarditis.

SUMMARY

The syndrome of constrictive pericarditis may be produced by neoplastic involvement of the pericardium. Such a process should be suspected when the

symptoms of predominant right-sided heart failure appear during the course of a malignancy, in the absence of other usual causes of such failure. A case of bronchogenic carcinoma with metastasis to the pericardium demonstrating this condition is reported.

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THE CURE OF SUBACUTE BACTERIAL ENDARTERITIS BY
SURGICAL LIGATION IN A PATIENT WITH PATENT
DUCTUS ARTERIOSUS COMPLICATED BY THE
PRESENCE OF MULTIPLE CONGENITAL
CARDIAC DEFECTS

REPORT OF A CASE

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IT IS generally agreed that the absence of typical murmurs constitutes a contraindication to surgical intervention in cases of suspected patent ductus arteriosus. However, since typical murmurs are absent in nearly a third of the cases, and the incidence of subacute bacterial endarteritis ranges as high as 50 per cent in reported series, there must consequently be a considerable number of cases in which the decision for or against surgical treatment is difficult. A decision in favor of surgery may be made in such cases under two conditions. The first of these is that the infectious agent is resistant to sulfonamide or penicillin therapy. The second is that no other congenital defect is present which requires the open ductus as a compensatory mechanism.

It would seem reasonable to assume that the presence of multiple congenital defects would be a rather frequent cause for the occurrence of unusual physical signs, or the absence of typical findings, in cases of patent ductus arteriosus. In such instances excellent judgment is required in selecting a patient suitable for surgical treatment. A case is herewith reported in which an infected patent ductus occurred with atypical murmurs, in association with multiple congenital cardiac defects, in which the infectious agent was resistant to penicillin, and in which cure was accomplished by surgical ligation of the patent ductus arteriosus.

CASE REPORT

The patient, a 17-year-old white girl, was admitted to Henry Ford Hospital on April 14, 1944, with a chief complaint of persistent fever and "heart trouble." The present illness began approximately four months previously, at which time the patient experienced an influenza-like illness, the duration of which was three weeks. This was followed by recurrent bouts of fever, on occasion as high as 102° F. She had had fleeting abdominal pain, but no chest pain, night sweats, weight loss, or evidence of embolic phenomena in either systemic or pulmonary circulation. The past history was negative except for the presence of a heart murmur, known of since the age of six months, and episodes of paroxysmal tachycardia. The growth had been normal; exercise tolerance was average; and there was no history of rheumatic fever.

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Fig. 1.—X-ray of the chest before surgical ligation (May 23, 1944).

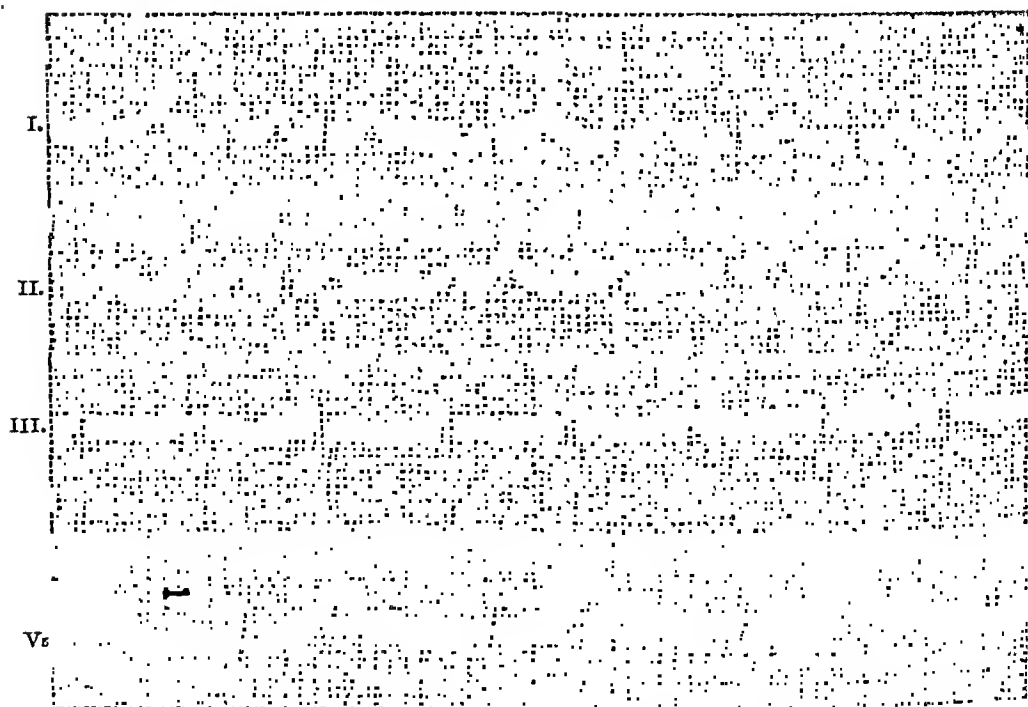


Fig. 2.—Electrocardiogram, taken May 23, 1944, showing inverted P waves in standard Leads I and II.

On physical examination the patient appeared to be a well-developed, well-nourished white girl of the stated age, who did not appear acutely ill. The head and neck were entirely normal. The mucous membranes were of good color. No petechiae were visible. There was no abnormal lymphadenopathy. On examination of the chest, the lung fields were resonant to percussion, the breath sounds were normal throughout, and no râles were heard. The heart was slightly enlarged to the left, the left border of cardiac dullness measuring 11 cm. from the midsternal line in the fifth intercostal space. There was no widening of the upper mediastinum. A systolic thrill was palpable over the base of the heart. On auscultation there was a loud, rough systolic murmur heard over the entire precordium, loudest at the second and third intercostal spaces at the left sternal border. This murmur was transmitted widely, and could be heard over the entire chest both anteriorly and posteriorly. The pulmonic second sound was accentuated, and there was a short diastolic blowing murmur heard at the third intercostal space at the left sternal border. The cardiac rhythm was regular. The blood pressure at rest was 120/60; immediately after exercise it was 120/40 to 10. Examination of the abdomen was essentially negative. The liver and spleen were not palpable. No abdominal masses or tenderness were noted. The extremities were normal. Pelvic examination was not done.

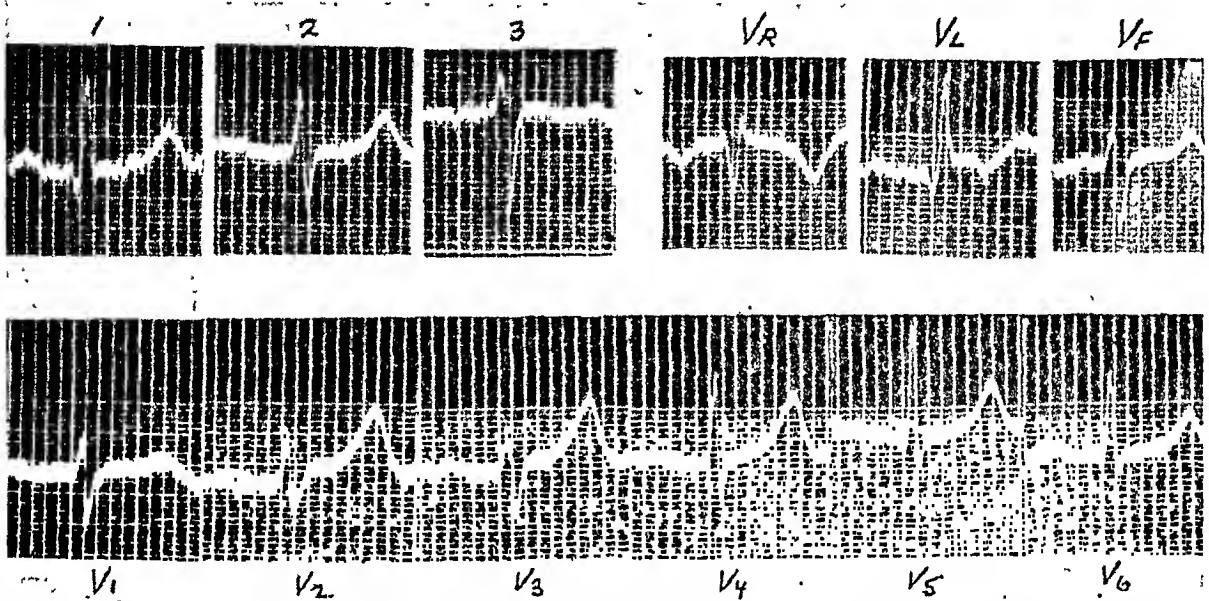


Fig. 3.—Electrocardiogram taken May 24, 1944. Standard extremity leads. Unipolar extremity Leads V_R , V_L , and V_F . Precordial Leads V_1 - V_6 .

The initial laboratory examinations included the following: Kline exclusion test, negative; hemoglobin, 13.1 Gm. per cent; erythrocytes, 4,370,000; leucocytes, 9,100 per cubic millimeter, with 65 per cent polymorphonuclear leucocytes and 35 per cent small lymphocytes; blood sedimentation rate, 38 mm. per hour; hematocrit, 43 per cent; urine specific gravity, 1.028, alkaline reaction, negative for albumin, sugar, casts, and red blood cells; blood nonprotein nitrogen, 28.1 mg. per cent; blood sugar, 78 mg. per cent; routine stool examination, negative. Two successive blood cultures were positive for hemolytic *Staphylococcus albus*.

Fluoroseopy of the chest revealed slight cardiac enlargement involving both ventricles, chiefly the left. There was increased amplitude of pulsation of the left ventricle, aorta, and pulmonary conus. The latter was not unusually prominent. There was partial obliteration of the aortic window. The transverse diameter of the heart measured 11.5 cm., and the internal transverse diameter of the chest measured 21.9 centimeters. The predicted transverse diameter of the heart (Hodges and Eyster) was 10.49 centimeters. The electrocardiogram showed left axis deviation ($R_1 + S_2 = 2.8$ mv.), with normal ventricular

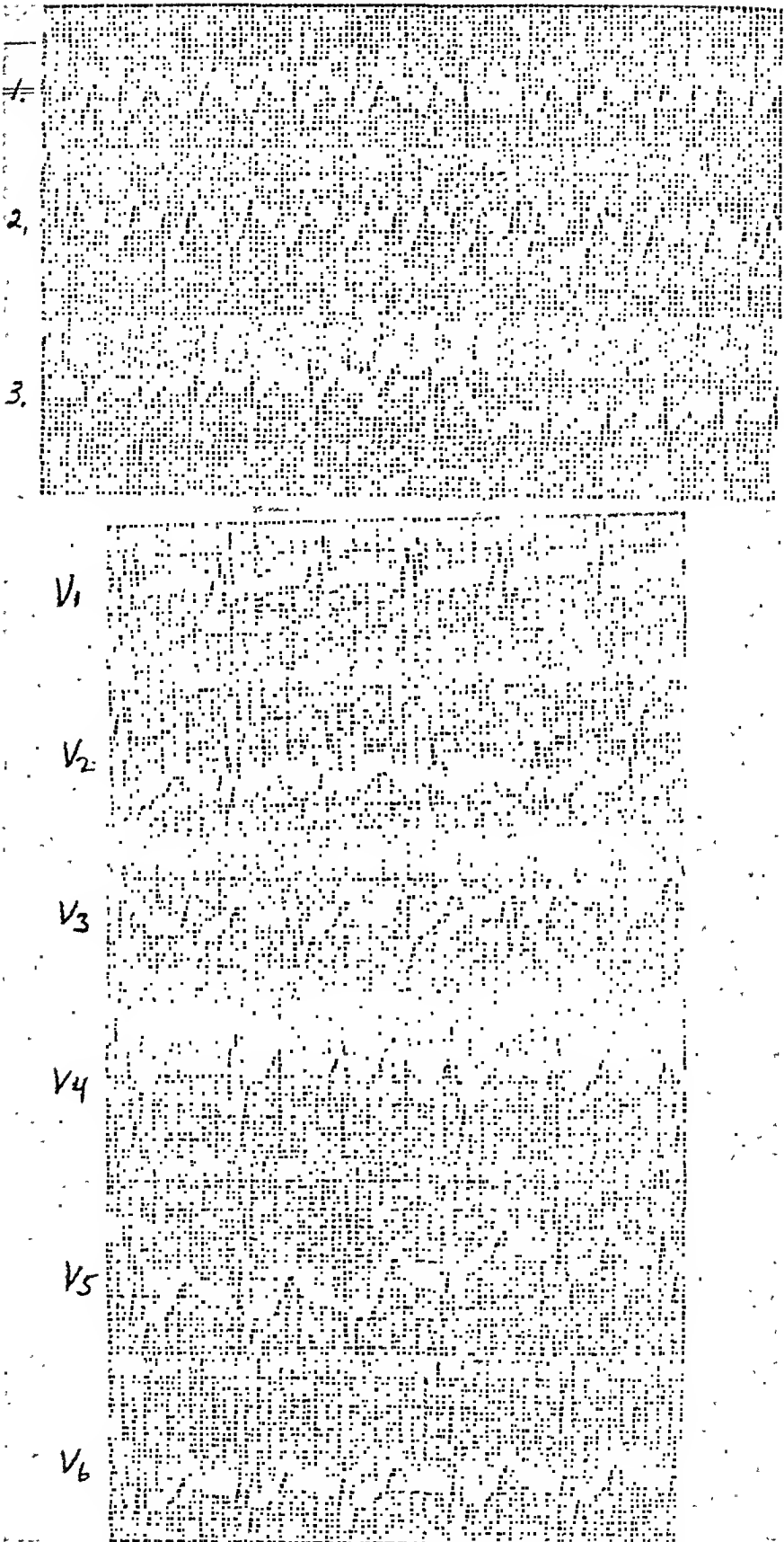


Fig. 4.—Electrocardiogram, taken Jan. 28, 1945, during paroxysm of auricular tachycardia.

complexes. P-R interval and QRS interval were normal. The form of the P waves varied considerably, on one occasion being inverted in standard Leads I and II (Fig. 2), on another occasion being normally upright (Fig. 3), and finally disappearing during a paroxysm of auricular tachycardia (Fig. 4). Phonocardiography proved the presence of the short diastolic murmur (Fig. 5). The initial venous pressure measured 9 cm. (saline) with no rise on right upper quadrant compression. The arm-to-tongue circulation time (decholin) measured 13 seconds; the arm-to-lung circulation time (ether) measured 8 seconds.

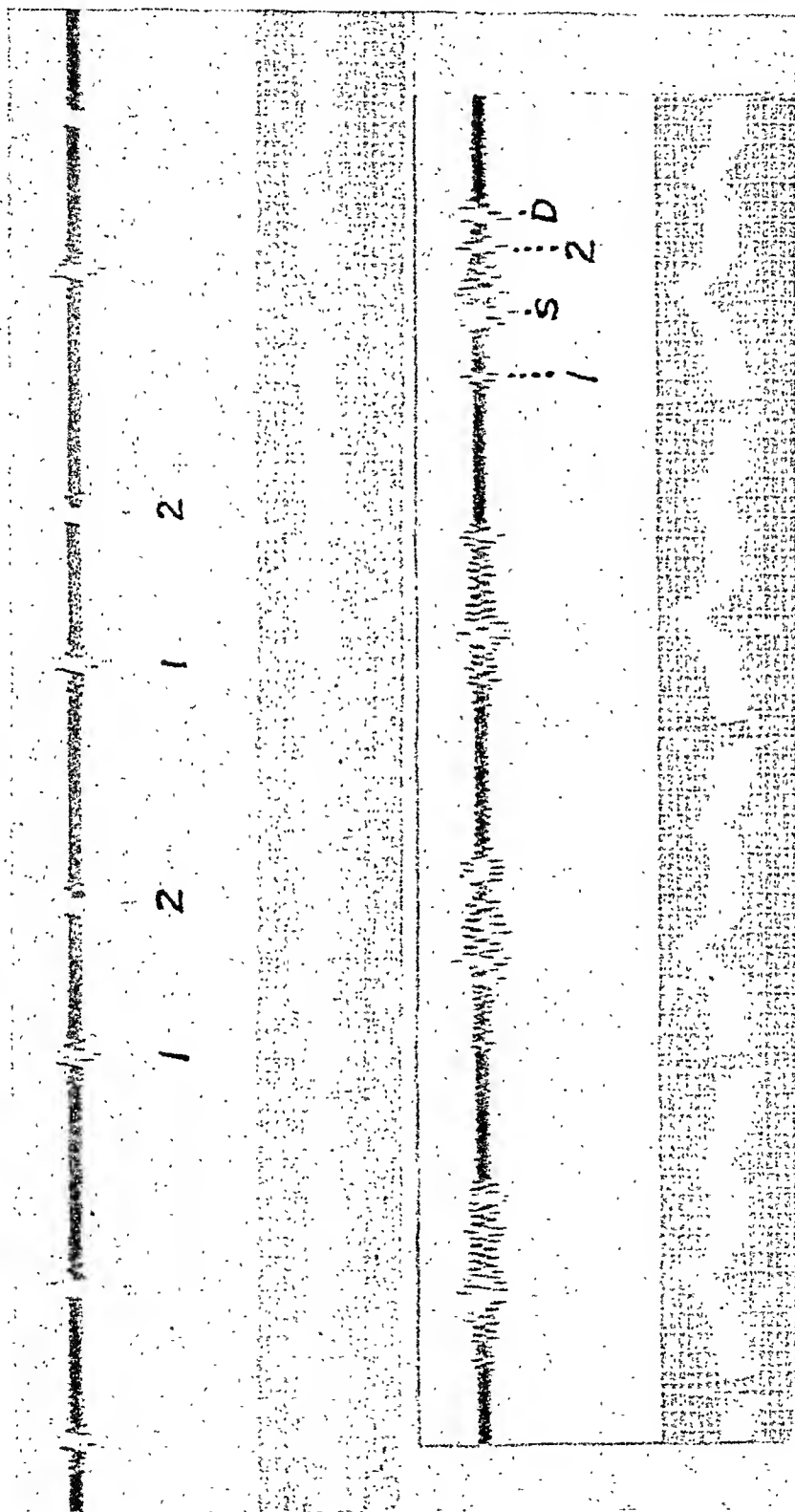


Fig. 5.—Simultaneous phonocardiogram and electrocardiogram taken preoperatively (lower record). Normal control above. 1, First heart sound; 2, second heart sound; S, systolic murmur; and D, diastolic murmur.

On the basis of the above findings the diagnosis of subacute bacterial endarteritis with patent ductus arteriosus was made. The presence of a concomitant congenital cardiac defect was considered likely.

Although the patient did not appear toxic or acutely ill, her temperature ranged daily between normal and 103.8° F. until the institution of penicillin therapy. The latter was begun on the twelfth hospital day and continued for twelve days prior to surgery. During the first twenty-four hours 200,000 units were given by continuous intravenous drip, subsequent dosage being 12,500 units intramuscularly every three hours, day and night.* Although the patient remained afebrile during this period, blood cultures after ten days of penicillin administration were still positive for hemolytic *Staphylococcus albus*.

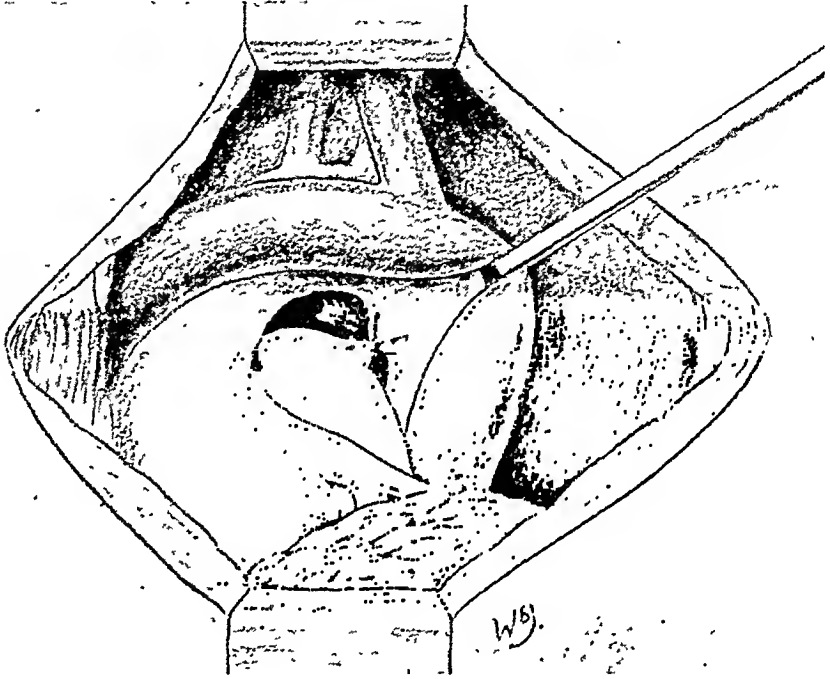


Fig. 6.—Artist's conception of operative field at time of surgical ligation. Anomalous left vena cava has been retracted from site of ligated ductus arteriosus.

On May 8, 1944, the patient was operated upon by Dr. Conrad R. Lam. The patent ductus was doubly ligated with heavy silk, after which a cellophane band was placed snugly around it. Considerable operative difficulty was encountered due to the presence of a large anomalous vein immediately overlying the aorta and the region of the ductus (Fig. 6). This appeared to be a left-sided vena cava. A palpable thrill, previously present over the ductus, disappeared immediately after ligation. Before operation the blood pressure measured 140/40; immediately after ligation it became 120/70. The surgical procedure was tolerated very well by the patient, and an uncomplicated recovery followed. Penicillin was administered for three days postoperatively and then discontinued. The patient remained afebrile and asymptomatic, and blood cultures have remained negative, the last one being taken on Feb. 5, 1945.

The physical findings on postoperative examination of the chest are of particular interest. The heart size did not decrease appreciably. There was still a very loud and widely distributed systolic murmur, but the maximum intensity over the lower right sternal border was louder and a systolic thrill was palpable at this point.

The pulmonic second sound was present but not accentuated, and the diastolic murmur, demonstrated preoperatively, was absent. The electrocardiogram was not essentially

*The penicillin used in this case was obtained through Dr. Roy D. McClure from Dr. Chester S. Keefer, Chairman of the Committee on Chemo-Therapeutic and Other Agents, Division of Medical Sciences, National Research Council.

different from that recorded prior to surgery. On fluoroscopic examination the cardiac silhouette had not changed appreciably, though the amplitude of pulsation seemed less marked. The venous pressure and circulation time determinations remained normal. A diagnosis was made of a patent interventricular septal defect.

The patient has remained well with the exception of occasional episodes of auricular paroxysmal tachycardia, now much less frequent than before surgery; and a ruptured ovarian cyst which required surgical excision Jan. 28, 1945. Her present physical condition is excellent; she has a perfectly normal exercise tolerance.

SUMMARY

A case of subacute bacterial endarteritis with patent ductus arteriosus, patent interventricular septal defect, and anomalous left vena cava, in which cure was effected by surgical ligation of the patent ductus, is reported.

Surgical treatment, when otherwise contraindicated by atypical physical signs, should be considered when the infecting organism is resistant to chemotherapy and when a complicating congenital defect, requiring a patent ductus as a compensatory mechanism, is not present.

MUMPS MYOCARDITIS

REVIEW OF LITERATURE AND REPORT OF CASE

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A RECENT paper by Wendkos and Noll¹ brought attention to the existence of acute myocarditis ascribable to mumps which could be recognized electrocardiographically during the convalescent period. In the case reported by them, however, no clinical signs of myocardial disease could be demonstrated. The purpose of this communication is to report a case, apparently of mumps myocarditis, which manifested both clinical and electrocardiographic evidences of myocardial involvement.

Scant attention has been given to the possibility of myocardial involvement during an acute episode of mumps. Pujol,² a French military surgeon, first suggested in 1918 that the virus of mumps might conceivably affect the myocardium. During a period of nine months he observed a total of 450 cases of mumps and in twelve of these he discovered some disturbances in the circulatory system. However, nine of these patients were eliminated from his consideration in view of other etiological factors for their heart disease. The remaining three patients complained of substernal pain and dyspnea during the convalescent period and, since no other explanation could be found, Pujol suspected myocardial involvement from mumps. Unfortunately, he did not have electrocardiograms to corroborate his suspicions. In 1932 Manca³ concluded from post-mortem observations that mumps may produce an acute interstitial myocarditis which could be distinguished from other forms by the fibrinous reaction which he believed to be peculiar to this disease.

Stimulated by these observations, Wendkos and Noll¹ undertook a random cardiac survey of fifteen soldiers convalescing from mumps. They demonstrated electrocardiographic changes in one patient (6.7 per cent) as manifested by sinus bradycardia, T-wave changes, and prolongation of the P-R interval. They further demonstrated temporary shortening of the A-V conduction time following the administration of atropine sulfate. This effect was interpreted as evidence that the prolonged P-R interval resulted from an increased vagal tone, a response similar to that observed in active rheumatic carditis.⁴⁻⁶ Complete recovery of their patient occurred in seven weeks.

The following case report is presented to point out both clinical and electrocardiographic evidences of acute myocarditis following mumps.

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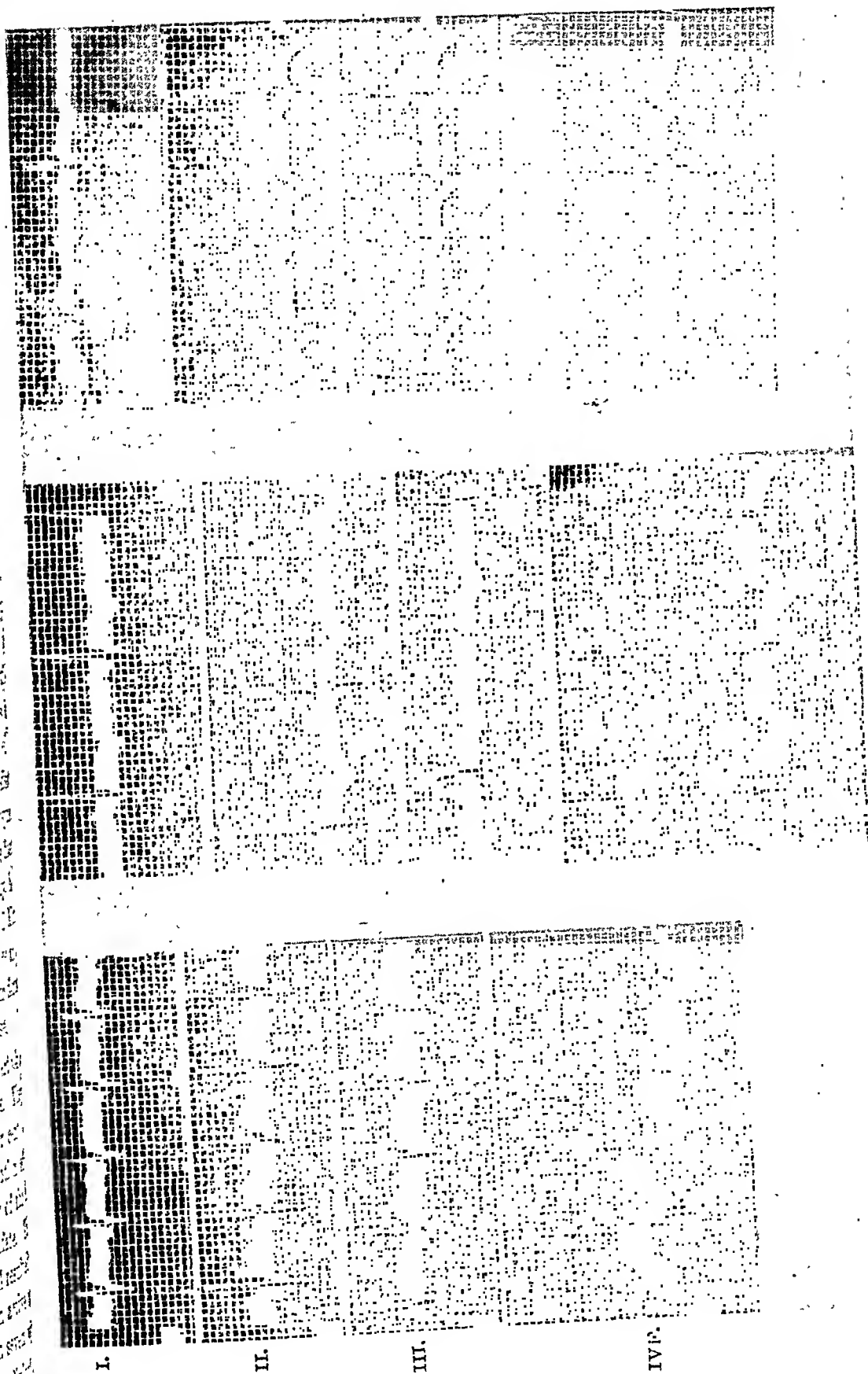


Fig. 1.—Electrocardiograms of a 14-year-old white boy with mumps and myocardial disease. A, Electrocardiogram made on March 27, 1944, eight days after the onset of parotid swelling. B, Electrocardiogram made on April 25, 1944, revealing slight change from previous one. (See text for complete description.) C, Electrocardiogram made on March 31, 1944, revealing acute myocarditis.

CASE REPORT

A. H., Jr., a 14-year-old white boy, entered Charity Hospital on March 26, 1944, complaining of fever, weakness, and swelling of both testicles. He stated that seven days previously his neck began to swell beneath the ears. The swelling attained considerable size. However, the patient did not go to bed and continued to be ambulatory. Three days later, the patient was forced to take to bed with high fever. The same day he developed soreness over the abdomen with intense pain on both sides of the abdomen extending from the border of the ribs downward to the inguinal regions. He felt nauseated and vomited several times. On the day of admission, both testicles began to swell.

Upon admission, physical examination revealed a well-developed, well-nourished white boy of the stated age who preferred to lie in bed on one side and maintained flexion of both legs. The temperature was 104° F., the pulse rate was 130, the respirations were 30 per minute, and the blood pressure was 100/70. The positive findings of the physical examination were as follows: slight swelling of the right parotid gland; muffled bronchovesicular breath sounds with a few râles in both bases posteriorly; a tachycardia (130 per minute) and a gallop rhythm at the apex; epigastric tenderness and mild lower abdominal tenderness; liver palpable 3 cm. below the right costal margin; bilateral testicular enlargement up to four times normal size; and a positive Babinski's reflex on the left side.

The laboratory data were as follows: leucocyte count of 12,930 per cubic millimeter with 90 per cent polymorphonuclears, 8 per cent lymphocytes, and 2 per cent monocytes; urinalysis, no abnormalities; carbon dioxide combining power of the blood, 30 volumes per cent; blood urea nitrogen, 19.6 mg. per 100 c.c.; fasting blood sugar, 129 mg. per 100 c.c.; negative blood Kline and Kolmer tests for syphilis; a negative blood culture; negative blood agglutination tests for *Eberthella typhi*, *paratyphi A* and *B*, *Brucella melitensis*, *Brucella abortus*, and *Bacillus proteus* X 19. A roentgenogram of the chest upon admission revealed an increase in the lung markings suggestive of an acute respiratory infection.

Because of the tachycardia and gallop rhythm at the apex, an electrocardiogram (Fig. 1, A) was taken and was interpreted by Dr. James L. Gouaux, cardiologist at Charity Hospital, as follows: auricular and ventricular rate 156 per minute; sinus tachycardia; slight slurring of the QRS complexes; slight shift upwards of the S-T segments in Leads I, II, and III; low T waves throughout with inversion of T₁ and T₂; and definite electrocardiographic evidence of myocardial disease. This was repeated seven days later (Fig. 1, B) at which time all T waves were inverted and the Q-T interval was at the upper limit of normal. This electrocardiogram was interpreted as compatible with subacute pericarditis and myocarditis.

The patient's course in the hospital was essentially uneventful. Because of somnolence, a spinal fluid examination was made which was within normal limits. The therapy was entirely supportive and symptomatic for mumps orchitis. The patient became afebrile on the third day and remained so until he was discharged on April 4, 1944.

He returned to the hospital on April 26, 1944, for a cardiac checkup. No pertinent physical findings were noted. The electrocardiogram (Fig. 1, C) was essentially the same as a previous one on April 4, 1944.

DISCUSSION

Evidence for the diagnosis of acute myocarditis in this patient is based upon the presence of a probable etiological factor, an acute onset, gallop rhythm at the apex, tachycardia, mild congestive heart failure as noted by enlargement of the liver and râles in the lung bases posteriorly, and clinical recovery within a few days. The electrocardiographic abnormalities persisted in this patient for a month. It is regrettable that we were unable to secure additional periodic observations on this patient.

Although too few cases of mumps myocarditis have been recognized to establish a clinical picture, it would appear that the myocarditis is nonspecific in nature and gives rise to symptoms and signs which differ in no respect from myocarditis from other causes. The exact incidence and the relation of this complication to the severity of the preceding parotitis are questions which remain unanswered. As Wendkos and Noll suggested, awareness of this condition may lead to increasing recognition. It seems plain, however, that cardiac surveys by all available methods of study should be undertaken on patients with mumps, and that the length of convalescence should be judged by the symptoms and findings of any cardiac disease, electrocardiographic studies, and periodic sedimentation rates.

SUMMARY

To our knowledge, this is the first case reported in the literature of myocarditis complicating mumps in which both clinical and electrocardiographic confirmation of the diagnosis could be made. No etiological cause for the myocarditis, other than mumps, could be determined.

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Abstracts and Reviews

Selected Abstracts

Bevans, M.: Changes in the Musculature of the Gastrointestinal Tract and in the Myocardium in Progressive Muscular Dystrophy. *Arch. Path.* 40: 225 (Oct.) 1945.

The author records the clinical and pathologic observations in four patients with progressive muscular dystrophy. In the voluntary muscles the changes were the recognized ones of progressive muscular dystrophy. While all four patients had myocardial lesions, only one patient showed in life clinical signs of heart failure, though all had tachycardia. The only electrocardiographic finding was right axis deviation, which two patients exhibited.

A composite picture of the gross myocardial lesions showed increase in, and opacity of, the myocardial fat, streaks of fibrosis throughout the myocardium, particularly the left ventricle, and slight focal thickening of the endocardium. Microscopic examination revealed a peculiar distribution of the scarring and of the areas of muscle degeneration. The most extensive lesions were seen near the epicardial surface, where the fibrous tissue which penetrated and replaced the myocardium appeared to be continuous with the epicardial fat or with the thickened epicardium. The myocardial fibers showed changes which were comparable to those seen in the skeletal muscles, although there were certain differences. Changes of a similar character were noted in various parts of the gastrointestinal tract.

BELLET.

Hiatt, E., Brown, D., Quinn, G., and Macduffie, K.: The Blocking Action of the Cinchona Alkaloids and Certain Related Compounds on the Cardioinhibitory Vagus Endings in the Dog. *J. Pharmacol. & Exper. Therap.* 85: 55 (Sept.) 1945.

The authors have determined and compared the plasma concentrations of certain cinchona alkaloids necessary to produce a blocking action on the cardio-inhibitory vagus endings in the heart of the dog. The alkaloids studied were quinine, quinidine, cinchonine, and cinchonidine. The conclusion of the authors is that of the alkaloids studied only quinidine effectively blocked the vagus endings at blood concentrations which, if applied to man, would not produce toxic effects. To effectively block the vagal endings it was necessary for quinine sulfate to reach a plasma concentration of 19.8 mg. per liter. The effective levels of cinchonidine and cinchonine sulfate were, respectively, 15.5 and 13.3 mg. per liter. Quinidine sulfate, on the other hand, was effective at an average plasma level of only 7.4 mg. per liter. The plasma levels of quinidine sulfate necessary for the successful treatment of auricular fibrillation and blocking the vagal endings are comparable.

BELLET.

Rappaport, A. E., Nixon, C. E., and Barker, W. A.: Fatal Thrombocytopenic Purpura Due to Sodium Salicylate. *J. Lab. & Clin. Med.* 30: 916 (Nov.) 1945.

A Negro man, 35 years of age, was given a total of 2,640 grains of sodium salicylate in thirty-three days. There were no untoward effects. After a drug-free period of fifteen days, the administration of sodium salicylate was resumed, and nine days later he showed the typical manifestations of thrombocytopenic purpura. Splenectomy failed to influence the hemorrhages. Further evidence of a toxic origin of the purpura consisted in the morphologic characteristics of the megakaryocytes and the metaplastic appearance of these elements in the spleen.

BELLET.

Barnes, Arlie R.: The Consideration of Two Cardiac Diseases Amenable to Surgical Treatment. *Journal-Lancet* 65: 382 (Nov.) 1945.

Barnes considers the minimal requirements for the diagnosis of patent ductus arteriosus to be, first, a continuous murmur (in the sense that there must be a diastolic as well as a systolic element), and second, roentgen evidence of some enlargement of the pulmonary conus. The diagnosis must be made with caution in the absence of an increased pulse pressure.

McMILLAN.

Gaston, E. A., and Folsom, H.: Ligation of the Inferior Vena Cava for the Prevention of Pulmonary Embolism. *New England J. Med.* 233: 229 (Aug.) 1945.

Since venous thrombosis is a disease that frequently affects the vessels of both lower extremities ligation of the inferior vena cava seems desirable, since this procedure not only interrupts the venous channel above an evident femoroiliac thrombosis, but also acts to prevent embolism from a simultaneous subclinical phlebothrombosis that probably exists in the veins of the opposite lower leg. The authors report two cases in which ligation of the inferior vena cava was performed below the level of the renal veins. Although an operation of some magnitude, it is compatible with recovery in seriously ill patients. A consideration of the available collateral pathways for venous return around the point of ligation indicates that eventual return to a normal venous pressure relation should ensue.

The indications for ligation of the inferior vena cava are not well defined. A pretty clear indication is the occurrence of several pulmonary emboli secondary to peripheral venous thrombosis. A review of the literature is also included in this report.

McM.

Segall, E. L., and Dorfman, W.: Death Following the Intravenous Administration of Papaverine Hydrochloride. *New England J. Med.* 233: 590 (Oct.) 1945.

Severe respiratory symptoms, hyperpnea, and tachypnea, developed in two patients within thirty seconds after the intravenous administration of papaverine. In both patients death occurred within five minutes. One patient, aged 80 years, had auricular fibrillation and, apparently, an embolism to the bifurcation of the aorta. The second patient, a 61-year-old woman, suffered from pulmonary embolism with infarction of the right lower lung lobe.

Since respiratory symptoms began so quickly, the authors feel justified in attributing death to the medication.

McM.

Levine, Samuel A., and Hindle, J. A.: Coronary Artery Disease Among Physicians. *New England J. Med.* 233: 657 (Nov.), 1945.

Levine and Hindle have attempted to secure statistical data bearing on the widely held opinion that coronary artery disease occurs more frequently in professional men, particularly physicians, than in other groups. They felt that a comparison of the age at the time of death from coronary artery disease in different groups would more accurately answer this question than would a consideration of the number of reported deaths.

Using 66.3 years as the average age of physicians at the time of death from all causes, their analysis showed that 65.8 years was the average age at death from coronary artery disease both in physicians and in the general population. The difference was not significant.

McM.

Drury, Alan N.: Observations Relating to Cardiac Hypertrophy Produced in the Rabbit by Arteriovenous Anastomosis, the Effect of Closure of the Anastomosis. *Quart. J. Exper. Physiol.* 33: 107 (May) 1945.

Drury carried out a series of studies on rabbits designed to show (1) whether the cardiac enlargement that develops after A-V anastomosis is the result mainly of hypertrophy or of dilatation and (2) whether or not this enlargement disappears after the A-V connection is abolished. From the experiments reported in this paper, as well as from earlier work, the author is satisfied that very real cardiac hypertrophy develops within six to eight weeks after

the establishment of an A-V anastomosis in rabbits. The hypertrophy disappears equally promptly after correction of the anastomosis. Only one animal showed any persistence of the hypertrophy. The author classifies hypertrophy which disappears as physiologic. The one example in which hypertrophy persisted after elimination of the A-V connection led the author to speculate as to whether physiologic hypertrophy may not become pathologic hypertrophy.

McMILLAN.

Burnett, C. H., Bland, E. F., and Beecher, H. K.: Electrocardiograms in Traumatic Shock in Man. *J. Clin. Investigation* 24: 687 (Sept.) 1945.

The authors hoped to obtain some information from electrocardiograms which would help to answer the question of whether the diminished cardiac output in shock is the result of cardiac involvement or is produced entirely by extracardiac factors. Thirty severely wounded soldiers were studied. Because of the conditions under which the studies were carried out and because many of the patients had chest wounds, chest leads were not made. Twenty-five of these thirty patients, all in marked and some in profound shock, showed no electrocardiographic changes. Some of the electrocardiographic abnormalities that were present in the remaining five patients are of interest. In two there was definite inversion of the T waves in Lead I, which disappeared within one hour after blood transfusion and a resulting rise of blood pressure. Both patients had wounds of the left chest but no evidence of actual cardiac or pericardial injury. Right axis deviation was anticipated as a result of the free use of fluids but was encountered only once. A fourth patient, who did not survive and may well have had some injury to the heart or pericardium, showed notched QRS complexes of low voltage in all leads. The fifth patient presented transient auricular fibrillation, with short runs of superimposed ventricular tachycardia. The conclusions to be drawn from this study are essentially negative and the authors emphasize as significant that twenty-five patients showed no electrocardiographic changes and only five exhibited any abnormality.

McMILLAN.

Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever. *Arch. Int. Med.* 76: 131 (Sept.) 1945.

The authors summarize four types of evidence which in the past twenty years have made it "increasingly apparent that infection by hemolytic streptococci is in some way related to the development of the rheumatic state." In their own series of 1,500 cases of respiratory infection they found 15 cases of rheumatic fever among 410 convalescents from streptococcal infections and no cases of rheumatic fever among the other 1,100 convalescents from nonstreptococcal infections.

The authors noted that among these patients rheumatic fever may follow streptococcal infection without any intervening latent period. In such patients, fever, fatigability, anorexia, weight loss, and persistent elevation of the sedimentation rate gave evidence of continued disease immediately following the frank streptococcal infection. During this period, many of these patients exhibited electrocardiographic changes including inversion of T waves and prolongation of the P-R interval. These electrocardiographic changes, however, were also found in some of the apparently normal convalescents from streptococcal disease.

In conclusion, a plea is made for the examination of rheumatic subjects for circulating antibodies or tissue hypersensitivity to streptococcal proteins in a more pure state than has been available heretofore.

T. N. HARRIS.

Rinehart, J. F.: Observations on the Treatment of Rheumatic Fever With Vitamin P. *Ann. Rheumat. Dis.* 5: 14 (Sept.) 1945.

The purpose of this paper is to report observations which were made on 39 cases of rheumatic fever which have been treated with vitamin P for one month or longer. Of the 39 patients, 24 were children and 15 were adults. All showed activity of the rheumatic process at the time treatment was instituted, and many were of the polycyclic or refractory type. The preparation used in most cases was crude hesperidin, 0.5 Gm., fortified with 20 mg. of hesperidin methyl chalone. The usual dose was 1.5 Gm., one tablet, three times daily with

meals. No toxic or ill effect was noted. The vitamin P was given in all cases as additional therapy.

Twenty-six of the 39 patients had exhibited persistent rheumatic activity for six weeks or longer. One month after the institution of treatment, their sedimentation rate had fallen from an average of 33 mm. to 17.5 mm. per hour. Thirty-four patients exhibited significant slowing of the sedimentation rate by the end of six weeks. Twenty-two of the 39 patients showed either no evidence of activity or minimal activity after four to six weeks of therapy. These results, chiefly in terms of slowing sedimentation rate but paralleled by other clinical manifestations of improvement, are considered evidence that vitamin P exerted a beneficial influence on the course of the illness.

LAPLACE.

Bedell, A. J.: Clinical Differentiation of Emboli in the Retinal Arteries From Endarteritis. Arch. Opth. 34: 311 (Oct.) 1945.

This paper is a summation of the study and correlation of cases of sudden blindness caused by the abrupt closure of the central retinal artery or one of its branches, and its purpose is to facilitate the differentiation of embolism of the retinal artery from endarteritis. Illustrative case reports are presented. The diagnostic criteria for embolism of the central retinal artery, on the one hand, are contraction of the arteries to threadlike size, great reduction in size of the veins, frequent visibility of the wall of the artery, and retinal edema limited to an oval area. It is characteristic of retinal endarteritis, on the other hand, that the arteries are rarely as small as those found in cases of embolism, that there are always white plaques along their walls, and that the retinal edema involves the entire visible fundus. In both embolism and endarteritis, the optic nerve appears white, atrophic, and sharply outlined.

LAPLACE.

Smithwick, R. M.: Experiences With the Surgical Treatment of Essential Hypertensive Cardiovascular Disease in Man. Cleveland Clin. Quart. 12: 105 (Oct.) 1945.

The operation employed by the author consists of a two-stage sympathectomy involving removal of sympathetic trunks from at least the tenth dorsal through the first lumbar, inclusive, at most from the sixth dorsal through the third lumbar, inclusive, and usually from the eighth dorsal through the first or second lumbar. In all cases the great splanchnic nerves are removed from the celiac ganglia to the mid-thoracic region, and divided rami are carefully clipped with silver dural clips to guard against regeneration. Postoperative postural hypotension is a valuable sign indicating that important pathways have not been overlooked, and its presence in cases where the operation fails makes it reasonably certain that inadequate surgery is not the explanation. Postural hypotension usually disappears in a few months.

In a six-year period, over 600 unselected patients were operated upon. The operative mortality was 2.2 per cent: 2 per cent within one year of operation and 3.6 per cent one or more years after operation. Nearly two-thirds of the deaths occurred in patients who had a resting diastolic pressure of 140 mm. or more, together with such manifestations as advanced eye ground changes, encephalopathy, and poor cardiac or renal function. Operation in such cases now seems very rarely advisable. The majority of a series of 179 unselected patients observed for a period of one to five years were improved. Beneficial effects included changes in the eye grounds, electrocardiogram, and cardiac and renal functions as well as subjective improvement. The diastolic pressure was lowered 30 mm. or more in 42 per cent of the cases, 20 to 29 mm. in 18 per cent, 10 to 19 mm. in 20 per cent, and 0 to 9 mm. in 12 per cent. In 8 per cent of the cases the blood pressure was higher. Studies are now in progress to determine criteria by which the outcome of operation may be anticipated. Results indicate, for example, that women are better subjects than men.

Among the patients who were operated upon, two were found to have pheochromocytoma. Both had severe hypertension of the narrow pulse pressure variety which was nonparoxysmal. Their blood pressure returned to normal and they have continued to do well for several years after operation.

LAPLACE.

Groedel, F. M.: The Pneumocardiogram. *Exper. Med. & Surg.* 3: 361 (Nov.) 1945.

The author describes pneumocardiography as the technique of obtaining a record of the pressure changes within the thorax which are created by and which accompany each heartbeat. The literature is reviewed and the conclusion cited that there is no fundamental difference between the recorded curves of pressure (pneumocardiogram) and those of air velocity (pneumotachogram) as the typical points of inversion of the curves in both are found to be identical. The author's technique for recording the pneumocardiogram consists in utilizing an anesthesia mask, the outlet of which is directly connected with a microphone by 3 cm. of rubber tubing. The chief technical difficulty is that of teaching the patient to open his glottis while the record is being made.

The physiologic basis for the various deflections of the pneumocardiogram is still largely controversial, and further careful work on the subject is desirable. The author found, however, that the cardiopneumographic peaks can be very well timed and explained on the basis of the phlebogram. The cardiopneumogram was, in fact, found to be almost identical in normal cases with a phlebogram obtained by means of a receiver bell loaded with 300 grams. The conclusion is reached that both consist of air- and venous-blood tidal waves which represent the pressure changes in the thorax due to the blood in- and outflow, and of superimposed air- and venous-blood concussion waves which reflect the various mechanical events in the heart.

LAPLACE

Kottke, F. J., Kubicek, W. G., and Visscher, M. B.: The Production of Arterial Hypertension by Chronic Renal Artery-Nerve Stimulation. *Am. J. Physiol.* 145: 38 (Nov.) 1945.

Since reducing the blood flow to the kidneys by mechanical constriction of the renal arteries produces hypotension, it seemed desirable to ascertain whether decreasing renal blood flow by stimulation of renal vasoconstrictor nerves might likewise cause an elevation of blood pressure. The studies reported were carried out on dogs. Electrodes were placed around one or both renal arteries and their accompanying nerves. In the acute experiments, the dogs were anesthetized, the blood pressure was recorded directly, and the renal blood flow was estimated by a thermostromuhr. Electrical stimulation with various types and frequencies of current was effective in producing renal vasoconstriction. There was, however, no significant increase in arterial pressure, even with a 75 per cent reduction of renal blood flow for as long as two hours. In the chronic experiments, arterial pressure was recorded indirectly by employing a Van Leersum loop around the left carotid artery. Shielded unipolar silver electrodes were applied to each renal pedicle, using aseptic technique. The leads were brought out through a stab wound in the back, and the animal was allowed to recover. A sinusoidal alternating current of 2 c.p.s. was applied for twenty to twenty-two hours daily. This procedure was effective in producing arterial hypertension with pressures as high as 238/194, and, in one animal, a convulsive state associated with elevated blood creatinine. Hypertension was maintained for as long as twenty-seven days but subsided when the continuous stimulation was withdrawn.

There was no evidence that a persistent hypertension could be produced by the means described. On the basis of these studies, the authors state that hypertension of the type produced by chronic renal artery-nerve stimulation does not appear to be a simple hemodynamic consequence of renal vasoconstriction.

LAPLACE

Parkinson, John: The Harveian Oration on Rheumatic Fever and Rheumatic Heart Disease. *Lancet* 249: 657 (Nov.) 1945.

The first part of the oration deals mainly with the diagnosis of early rheumatic heart disease. Parkinson states that, whereas too much emphasis was once placed on systolic murmurs, the pendulum may now have swung too far in the other direction. Any fairly

obvious systolic murmur should be looked upon critically. Roentgenology is at present of great help in recognizing rheumatic heart disease in its early stages. No method of study, however, eliminates the necessity of basing one's decision as to whether a systolic murmur is organic or incidental mainly upon the quality of the murmur. "The louder, the longer and the more constant the murmur, the more likely it is to represent organic change." Many typical examples of mitral stenosis show only a systolic murmur, although there is nearly always associated roentgen evidence of some left auricular enlargement.

The second part of the oration is devoted to the "Problems of Rheumatic Fever." In Great Britain, 2.6 per cent of the child population of London are estimated to have had this disease, and probably 16,000 persons out of a population of forty million die of the disease and its sequelae yearly. Parkinson feels that rheumatic fever has the ability to produce immunity and subscribes to the view that a large proportion of the population have at one time had the disease in a minimal or subclinical form and are partially immune.

Concerning the etiological role of hemolytic streptococci, the author believes that "while there is some causal relation between the streptococci and rheumatic fever, the streptococcus is not the essential cause." He is of the opinion that one cannot dismiss the possibility that some specific organism, at present unidentified, may prove to be the cause of rheumatic fever. A chief reason for this point of view is the almost specific involvement of the mitral valve by rheumatic fever, which is unlike the behavior of other known streptococcal diseases, particularly scarlet fever.

The debated question of the advisability of removing tonsils is discussed. Parkinson expresses the view that, if the tonsils are visibly infected and if the tonsillar glands are enlarged, they constitute a greater danger to rheumatic than to other children. McMILLAN.

Ben-Asher, S.: The Treatment of Anginal Syndrome With Thiouracil. J. M. Soc. New Jersey 42: 401 (Dec.) 1945.

The benefit in cases of angina pectoris which is obtained by total thyroidectomy suggested that a similar result might be obtained by the administration of thiouracil. Such a result was actually observed by the author in 1943 in the course of treatment of a case of hyperthyroidism in which anginal pain subsided when thiouracil was successfully used in reducing the metabolism. Since then the author has employed thiouracil in the treatment of eight patients who had angina pectoris. Electrocardiographic abnormalities were present in all cases. The basal metabolism was slightly elevated in one case and normal in seven cases. Each patient was given 0.6 Gm. of thiouracil daily for two weeks, followed by a maintenance dose of 0.2 Gm. daily. No other medication was given except nitroglycerin for relief of pain during an attack. By the criterion of relief of pain in the course of ordinary daily activity, the author considers that the treatment was beneficial in all cases. The results are graded as excellent in two cases, good in five cases, and fair in one case. In all cases the basal metabolic rate was reduced to -8 to -20 per cent at the time of maximum improvement. In five cases improvement was maintained after thiouracil therapy was stopped, and in two cases a relapse occurred within six to eight weeks after changing from thiouracil to a placebo. The author emphasizes the fact that spontaneous improvement is common in the course of angina pectoris, but he believes that the results of thiouracil therapy are, nevertheless, sufficiently impressive to warrant further investigation of this form of treatment. LAPLACE.

Kinney, Thomas D., Sylvester, R. E., and Levine, S. A.: Coarctation and Acute Dissection of the Aorta Associated With Pregnancy. Am. J. M. Sc. 210: 825 (Dec.) 1945.

The authors could find only two previously recorded instances of combined coarctation and dissection of the aorta. They report a third example which is the first case in which a complete diagnosis was made ante mortem. The diagnosis of coarctation was suggested chiefly by arterial pulsation in the back and the absence of palpable pulsation of the abdominal aorta and femoral arteries. The principal finding that suggested dissecting aneurysm was the

sudden onset of pain in the throat and upper back. An enlarging cardiac silhouette, demonstrated by roentgenogram and certain abnormalities in the electrocardiogram added further confirmation.

At necropsy changes in the aorta which were compatible with idiopathic medial cystic necrosis were present proximal to the coarctation, but were not present distal to the obstruction. Reports by other observers of this pathologic lesion in association with coarctation, both with and without dissection, are cited.

McMILLAN.

Race, George A., and Lisa, James R.: Combined Acute Vascular Lesions of the Brain and Heart, A Clinical-Pathologic Study of Fifteen Cases. *Am. J. M. Sc.* 210: 732 (Dec.), 1945.

Race and Lisa analyzed the necropsy findings of one hundred consecutive patients in whom acute vascular lesions of either the brain or heart were present. In 15 patients both myocardial infarction and either diffuse petechial cortical hemorrhage or massive cerebral hemorrhage were found. They feel that this combined involvement is neither infrequent nor coincidental, and suggest that cerebral anoxia secondary to the myocardial infarction may well have been responsible for the cerebral lesions. In support of this view, they point out that five additional patients with myocardial infarction presented, in life, evidence of cerebral lesions, though no cerebral involvement was found at necropsy.

The clinical picture was confusing. In all instances the neurological findings predominated and were more constantly recognized. In eight of the 15 patients cardiac involvement was unsuspected during life. Slightly more than 50 per cent of the 20 patients died of bronchopneumonia. The authors suggest that sulfonamides be given prophylactically when combined cerebral and cardiac lesions exist.

McMILLAN.

Sokolow, M., and Garland, L. H.: Cardiovascular Disturbances in Tsutsugamushi Disease. *U. S. Nav. M. Bull.* 45: 1054 (Dec.) 1945.

A study was made of 35 convalescent patients from the Southwest Pacific who had had tsutsugamushi disease three to six months previously. All of the patients had been ambulatory for a period of one to three months. The symptoms in all cases were strikingly similar and varied only in degree. The predominant symptoms were fatigability, weakness, dyspnea and palpitation on slight effort, and precordial pains. Dyspnea and palpitation were slight in approximately 60 per cent of cases, moderate in 30 per cent, and absent in 10 per cent. Examination of the heart involved occasional soft apical or pulmonic systolic murmurs but no evidence of valvular disease or pericarditis. There was no gross abnormality of the sounds and no evidence of congestive heart failure. A striking feature in one-third of the cases was vasomotor disturbance of the hands and feet, manifested by mottled coldness, clamminess, and acrocyanosis. The electrocardiogram was normal except for seven cases in which there were minor abnormalities such as slurred QRS complexes, low amplitude or flat T waves in Lead I, right axis deviation, and nodal and ventricular extrasystoles. The arm-to-tongue circulation time was normal in all cases. A few patients had minor decreases in vital capacity. However, the breath-holding tests were almost universally decreased, approximately 75 per cent of the patients failing to hold the breath for the normal time of forty-five seconds. Seven patients could not hold the breath longer than twenty seconds. A standard exercise test, consisting of twenty hops on each foot for a total of forty hops, was applied in 28 cases. The resultant dyspnea and palpitation were abnormal in 70 per cent of the cases and severe in 15 per cent. Blood pressure was normal, but two-thirds of the patients had abnormally rapid heart rates. X-ray examination revealed definite cardiac enlargement in four cases and questionable enlargement in two cases. Roentgenkymographic evidence of abnormal cardiac contractions was observed in 14 cases and consisted of slight to moderate "peaking" of ventricular waves in 14 cases, with shallow ventricular contractions in three cases. The course of the circulatory disturbances noted was progressively favorable,

and all of the men were able to proceed on furlough within ninety days prior to return to duty. Attention is called to the similarity of the convalescent circulatory manifestations of this disease and those reported for trench fever during World War I. LAPLACE.

Starr, I., and Mayock, R. L.: Convalescence From Surgical Procedures. I. Studies of the Circulation Lying and Standing, of Tremor, and of a Program of Bed Exercises and Early Rising. Am. J. M. Sc. 210: 701 (Dec.) 1945.

The purpose of this investigation was to search for objective abnormalities during convalescence from surgical procedures in order to explain why, during this period, patients do not feel as they do in health and are unable to perform certain tasks which in health would be easy for them. The studies employed included recording of pulse rate, blood pressure, and the ballistocardiogram, in both the horizontal and vertical positions. From the ballistocardiogram, the cardiac output was calculated and also an estimate made of the amount of tremor. Forty-four patients were studied in this manner before operation and during post-operative convalescence.

Twenty-five of the patients studied had been operated upon for hernia. They were in good physical condition before operation and the changes observed after operation could therefore be attributed to convalescence. These postoperative changes included, in the horizontal position, diminished cardiac output and late fall in blood pressure; and, in the vertical position, increased cardiac output and pulse rate and fall in systolic blood pressure. There was also an increase in the difference between the lying and standing pulse rate and the lying and standing cardiac output. The amount of tremor on standing was increased.

The remaining 19 patients studied had undergone more serious operations. They varied so much individually, according to the nature and severity of their illness, that averages of their results could not be considered significant. They showed, in general, the same trends as were found after herniorrhaphy, except where one of two factors entered into the situation. When large amounts of fluid were given intravenously, the usual postoperative fall of cardiac output was prevented and sometimes replaced by a rise. When the patient's ability to take food and fluids was improved by the operation (for example after gastrostomy for carcinoma of the pharynx), the postoperative course differed from the usual, and pulse rate, blood pressure, and cardiac output all tended to increase.

Ten of the patients operated upon for hernia were treated differently from the others. Beginning with the second postoperative day, they carried out a series of mild exercises. The patients lay in bed, exercised the arms and legs for five minutes, stood up for five minutes, then returned to bed and exercised again for five minutes. This procedure was repeated twice daily. These patients showed no significant difference from those who remained in bed, except that their blood pressure was slightly lower on the tenth day, at which time also the control group exhibited more tremor than the exercised patients, and three of them were unable to stand. The latter observations were indicative of better physical condition in the exercised patients, but the difference was apparent only on the one day. LAPLACE.

Starr, I., Mayock, R. L., and Battles, M. G.: Convalescence From Surgical Procedures. II. Studies of Various Physiological Responses to a Mild Exercise Test. Am. J. M. Sc. 210: 713 (Dec.) 1945.

The main purpose of this investigation was to answer the question as to whether or not the response to exercise is altered in postoperative convalescence. The authors speculated that during that period a given amount of work might be performed less efficiently than under normal circumstances. An easy weight-lifting test was designed which was carried out in the recumbent position and consisted in lifting a 10-pound iron bar from chest to arm's length thirty times in one minute. The subject breathed from a spirometer and the oxygen consumption and rate and volume of respiration were estimated before, during, and after the test. Pulse rate was counted and the ballistocardiogram was recorded. From the latter, estimates were made of cardiac output.

Tested in this manner, five healthy subjects exhibited, as reactions to exercise, an increase in oxygen consumption, respiratory volume, cardiac output, and heart rate, with a variable effect on respiratory rate. The work performed was approximately 600 foot pounds per minute and the mechanical efficiency averaged 12.7 per cent.

Twelve patients operated upon for hernia and eight operated upon for other causes, were tested in the same manner before and after operation. It could not be demonstrated that convalescence had any significant effect on the amount of oxygen consumed, the mechanical efficiency, the volume of respiration, the cardiac output, or the pulse rate during exercise. However, when attention was given to the duration of the changes induced by the exercise, the averages showed significant differences, the increased oxygen consumption, respiration, and pulse rate declining to a resting level more slowly during convalescence than before operation. These differences however, could only be demonstrated by the use of averages. It is pointed out that the variability of the responses of individual subjects is so great that there appears to be no possibility of designing a satisfactory test of the type employed in this study, for the detection of convalescence and its duration.

LAPLACE.

Steiner, Sylvan A.: The Typical Headache of Essential Hypertension. Etiologic Considerations and Report of a New Form of Therapy. *M. Ann. District of Columbia* 14: 531 (Dec.) 1945.

The author points out that there is an abundance of evidence that the "typical" headache of essential hypertension may be of psychogenic origin and possibly may not be produced by the elevated arterial tension per se. Hypertensive headache bears a striking resemblance to migraine, and the apparent relationship between the two suggested the use of ergotamine therapy for hypertension. In addition, because hypertensive headache usually occurs during sleep in the horizontal position, it was decided to investigate the effect of sleeping in a bed, the headposts of which were raised on 10-inch blocks. Twelve cases of hypertension with headache in which treatment involved elevation of the head of the bed, were reported. The patients had previously used nicotinic acid, phenobarbital, thycyanates, and other medication without relief. Sleeping in the tilted bed, however, gave dramatic relief in ten of the twelve cases. One patient was considered a partial failure, being unable to sleep with more than a 5-inch elevation of the head of the bed. Four patients required oral ergotamine therapy and obtained complete relief after a week's course of medication.

LAPLACE.

Wedum, B. G., Wedum, A. G., and Beaghtler, A. L.: Prevalence of Rheumatic Heart Disease in Denver School Children. *Am. J. Pub. Health* 35: 1271 (Dec.) 1945.

Rheumatic heart disease is now the first cause of death, excepting accidents, among children aged 10 to 14 years, in Colorado as well as in the entire United States. Denver had the second highest death rate from rheumatic heart disease in children aged 5 to 14 years among the 25 largest cities in the United States during 1939 and 1940. Among children in Denver there has been no apparent decrease in the incidence of rheumatic fever. In connection with the activities of the Denver Area Rheumatic Fever Diagnostic Service, the authors undertook a study in which they personally examined 1,845 Denver high school girls. In this group a diagnosis of rheumatic heart disease was established in 1.63 per cent. In contrast with the incidence of rheumatic heart disease which was found by the authors, an incidence of only 0.48 per cent was reported when a series of 1,318 Denver school children was examined routinely by school physicians. The authors suggest, therefore, that public health officers, in all except the climatically favored southern part of the United States, should revise their conception of the amount of rheumatic heart disease in school children and regard it as 15 to 40 cases per 1,000 rather than 2 to 15.

The authors consider that the incidence of rheumatic heart disease and rheumatic fever in Denver is not disproportionately high as compared with other large northern cities, but it appears possible that the disease itself may be relatively more severe.

LAPLACE.

Book Reviews

THE CARDIO-PULMONAL FUNCTION DURING PREGNANCY. By Gerhard Widlund, University Clinic of Obstetrics and Gynecology, Upsala Sweden, 1945. Privately printed, 125 pages.

In studying many simple cardiorespiratory functions during pregnancy, it has repeatedly been found that many of them present so marked variations that it was difficult to establish definite trends as the effect of pregnancy.

The present work is a painstaking, statistical study of oxygen consumption, ventilation, blood pressure, and heart rate in pregnancy, and of the response of pregnant women to work tests. The study includes a critical survey of the important literature on the subject.

The author has performed 488 examinations on 157 women after rest and after graded exercises; for controls he used 60 healthy nonpregnant women of childbearing age.

He confirmed the generally accepted increase in oxygen consumption as pregnancy advances. This was associated with an increase in ventilation through increase in respiratory depth. There was also an increase in vital capacity, but not commensurate with the increase in respiratory depth; consequently, the "functional elasticity" with respect to ventilation depth was diminished.

He verified a slight increase in systolic and diastolic blood pressure and definite increase in heart rate toward the end of pregnancy. The difference between the heart rate when lying down and when standing up is diminished during pregnancy and increased in the puerperium. The reason for this difference is discussed. The oxygen consumption per work-time unit for a given amount of work was the same in pregnant and nonpregnant women, except on severe effort which was accomplished less economically by pregnant women.

The author finally concluded that, in regard to all investigated functions, a pregnant woman at rest behaves similarly to a nonpregnant woman doing moderate work; that is, already at rest, she partly utilizes her reserves.

The work is a creditable contribution to a fundamental but neglected problem.

JULIUS JENSEN, M.D.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 31

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No. 3

FRED M. SMITH

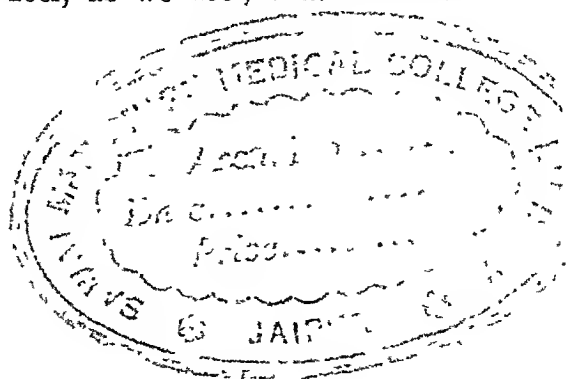
1888—1946

ON FEB. 23, 1946, Dr. Fred M. Smith died suddenly at his home in Iowa City. It is fitting that this public announcement of his death can be made in this JOURNAL, which until very recently he edited with great distinction.

Doctor Smith's death will bring a sense of sadness and regret to many persons: to those who knew him as a teacher, to those who knew him as a physician, and particularly to those who were privileged to know him as a friend.

Fred Smith's was a peculiarly full though short life: a life that hardly any conscientious physician can fail to envy. His contributions to medicine as a teacher, as a writer, and as an investigator were very substantial. He will be remembered for many reasons. Probably he will be best remembered for his contribution to our knowledge of the disease which finally claimed him and for his utter devotion to his profession, which in his code had higher precedence than his life.

Although this brief notice is being sponsored only by the American Heart Association, by the Editorial Board of the AMERICAN HEART JOURNAL, and by The C. V. Mosby Company, the sentiments which it expresses will be felt very poignantly by the many persons who came under the spell of Doctor Smith's influence. They will feel, as we feel, that American medicine has suffered a great loss.



Original Communications

A STUDY OF THE SUBJECTIVE SENSATIONS ASSOCIATED WITH EXTRASYSTOLES

EDWARD M. KLINE, M.D., CLEVELAND, OHIO, AND
LIEUTENANT (J.G.) THOMAS G. BIDDER, USNR

IT HAS been the general opinion that the subjective sensations sometimes associated with extrasystoles were produced by the first normal heartbeat following the compensatory pause. This beat is an unusually large one, owing to the increased filling of the heart during the long diastole. This explanation seemed so logical to the authors that no particular thought was given to other possible mechanisms until Ungerleider and Gubner¹ proposed that the sensations were due to the premature beat itself. White, referring to the symptoms associated with extrasystoles, writes, "Often, however, the occurrence of the premature beat is felt as a more or less disagreeable sensation, due less to the abnormal beat itself than to the pause which follows it, to the vigorous thump of the first normal beat after the pause, or to the pressure wave forced up into the neck veins from the right auricle at the time of the premature beat; this pressure wave results from the contraction of the auricles while the ventricles are in systole."²

In an effort to settle the matter conclusively it was decided to study individuals who experienced some type of subjective symptoms with their extrasystoles. Many persons were seen who had vague precordial sensations and extrasystoles, but in these patients there was no close association between the extrasystoles and the subjective complaints. Many more were completely unaware of their extrasystoles. Eleven individuals were found who were conscious of practically all extrasystoles, and, in these persons, 167 premature beats were studied as a basis for this report. In nine persons ventricular extrasystoles alone were present; in one, auricular extrasystoles alone were present; and in the remaining subject both types were present. These individuals were asked to press a signal key the instant they experienced their customary symptoms. This signal (*C* in all figures) was recorded with a simultaneous electrocardiogram (*D*), phonocardiogram (*B*), and radial pulse tracing (*E* in all figures except Fig. 3).*

From the Department of Medicine, Western Reserve University, and Lakeside Hospital, Cleveland, Ohio.

Read by title at the Seventeenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 3 and 4, 1944.

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*For office testing without the aid of additional equipment, a simple arrangement can be worked out with any electrocardiograph. The machine is placed near enough to the patient so that his hand can rest comfortably on the standardization button. He then is instructed to press the button the instant he notices the sensation in his chest, and a record similar to that shown in Fig. 2, *F*, is obtained.

The subjects' reaction times were determined by tapping their precordia lightly with an instrument which recorded the time of contact (*A*, first deflection, all figures). The subjects then pressed a second button the instant they felt the instrument strike their chests (*A*, second deflection). The electrocardiograph was used to measure this interval, which was most often found to be about 0.2 second.

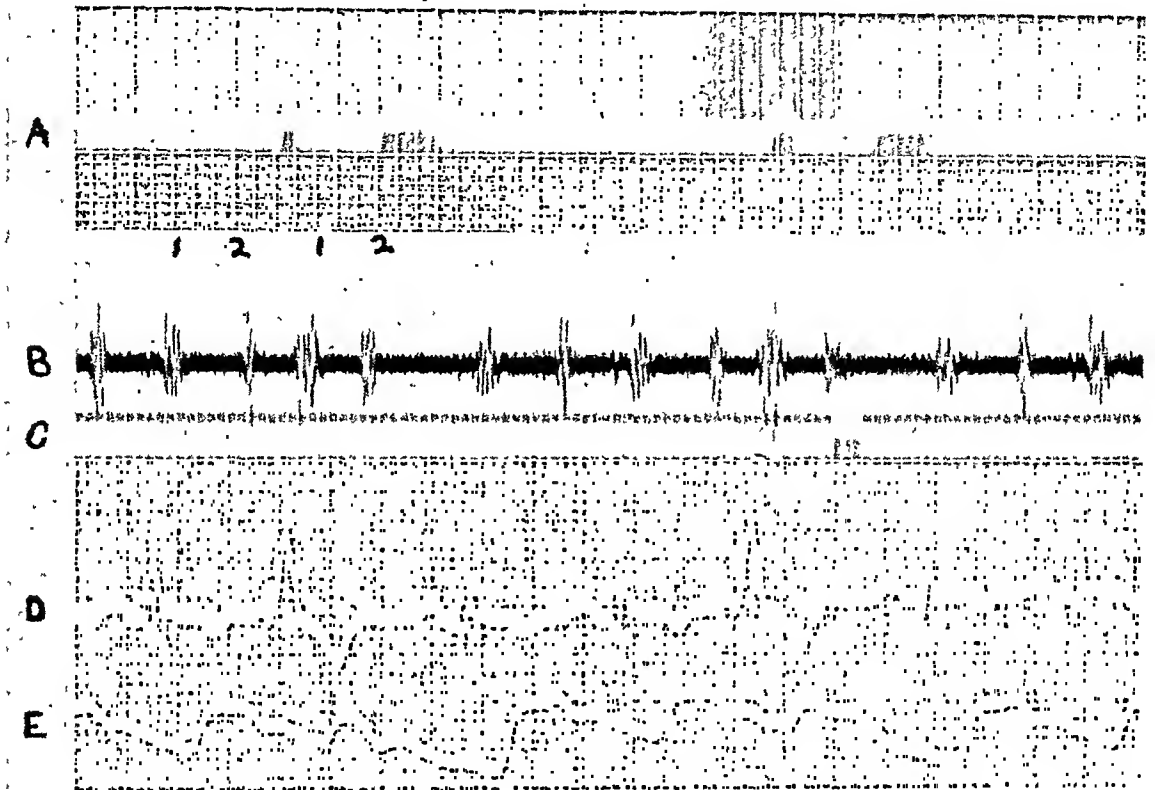


Fig. 1.—H. R. *A*, Test of reaction time. First deflection represents the contact of testing instrument with the precordium. The subject felt the contact and pressed the signal button at the time of the second deflection. Two tests are shown. *B*, Phonocardiogram. Note that the first sounds of the extrasystoles are louder than those of the normal beats. *C*, Signal indicating patient's awareness of extrasystoles. The first one was passed. *D*, Lead III; two ventricular extrasystoles are shown. *E*, Radial pulse tracing.

RESULTS

Our subjects reacted to the perception of their extrasystoles in a remarkably constant manner. This was unexpected; we had believed that we would get many types of reactions. Every subject pressed the signal key (*C* in all figures) during the pause after the premature beat (*D* in all figures) and before the appearance of the first normal beat. Therefore, it was not this unusually forceful beat after the pause that produced the symptoms, but rather either the premature beat itself or the compensatory pause which followed the premature beat.

There is nothing in our data to support the view that it is the pause that one notices. By inspection of the figures it can be seen that in each instance, the signal (*C*) was given considerably in advance of the time when the next normal beat was due. For example, in Fig. 1 the average R-R interval measures 0.60 second. The signal was given 0.32 second after the R wave of the second

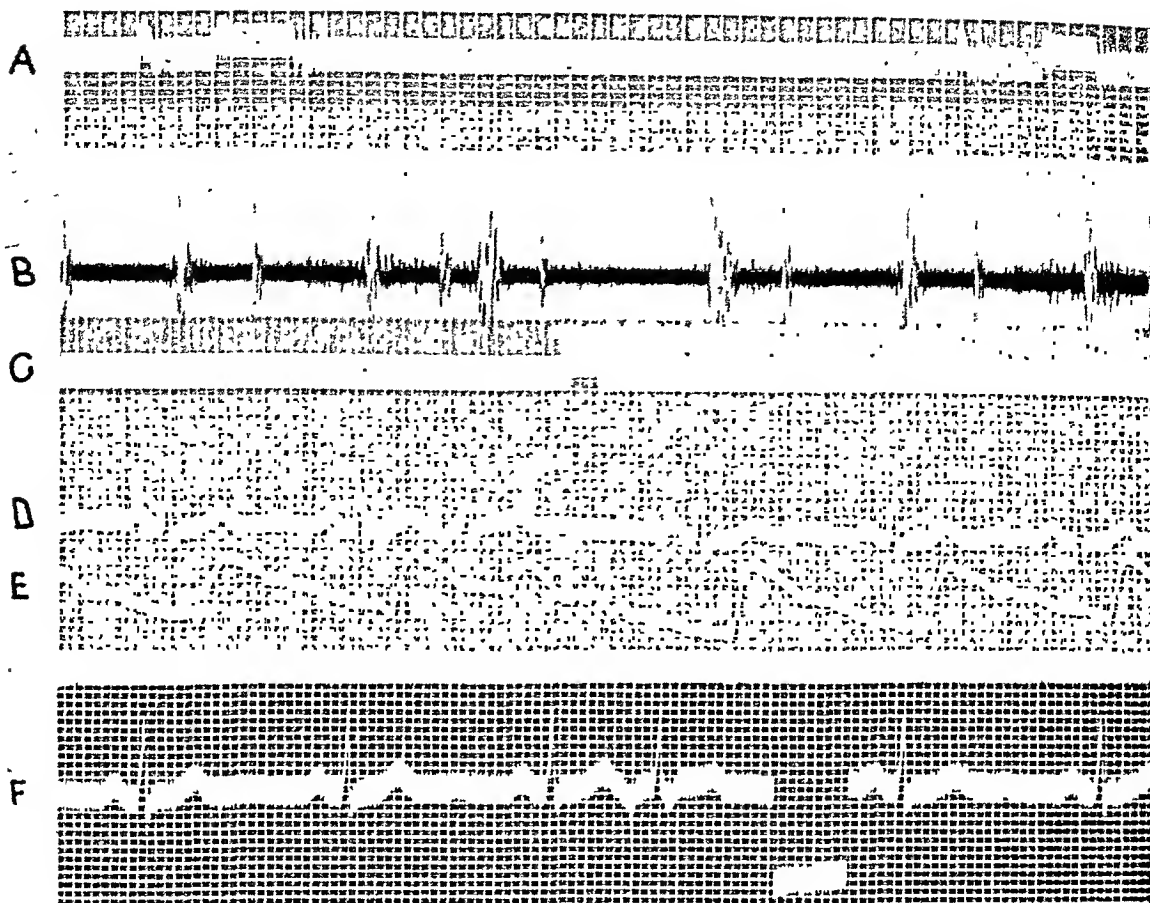


Fig. 2.—W. J. A, Test of reaction time. B, Phonocardiogram. C, Signal indicating subject's awareness of extrasystoles. D, Lead II; one auricular extrasystole is shown. E, Radial pulse tracing. F, Subject pressed electrocardiograph standardization button when extrasystole was noticed. Lead II; one auricular extrasystole is shown.

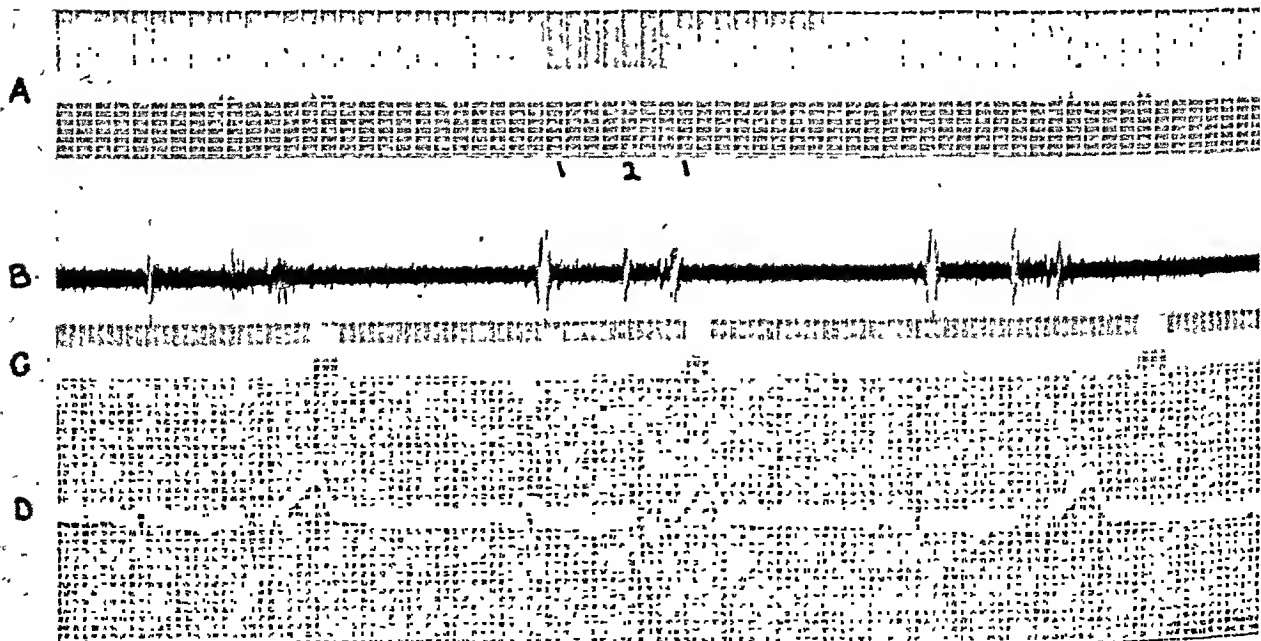


Fig. 3.—A. W. A, Test of reaction time. B, Phonocardiogram. Note that the first sounds of the extrasystoles are of smaller volume than those of the normal beats. C, Signal indicating subject's awareness of extrasystoles. D, Lead III, ventricular extrasystoles producing a bigeminal rhythm.

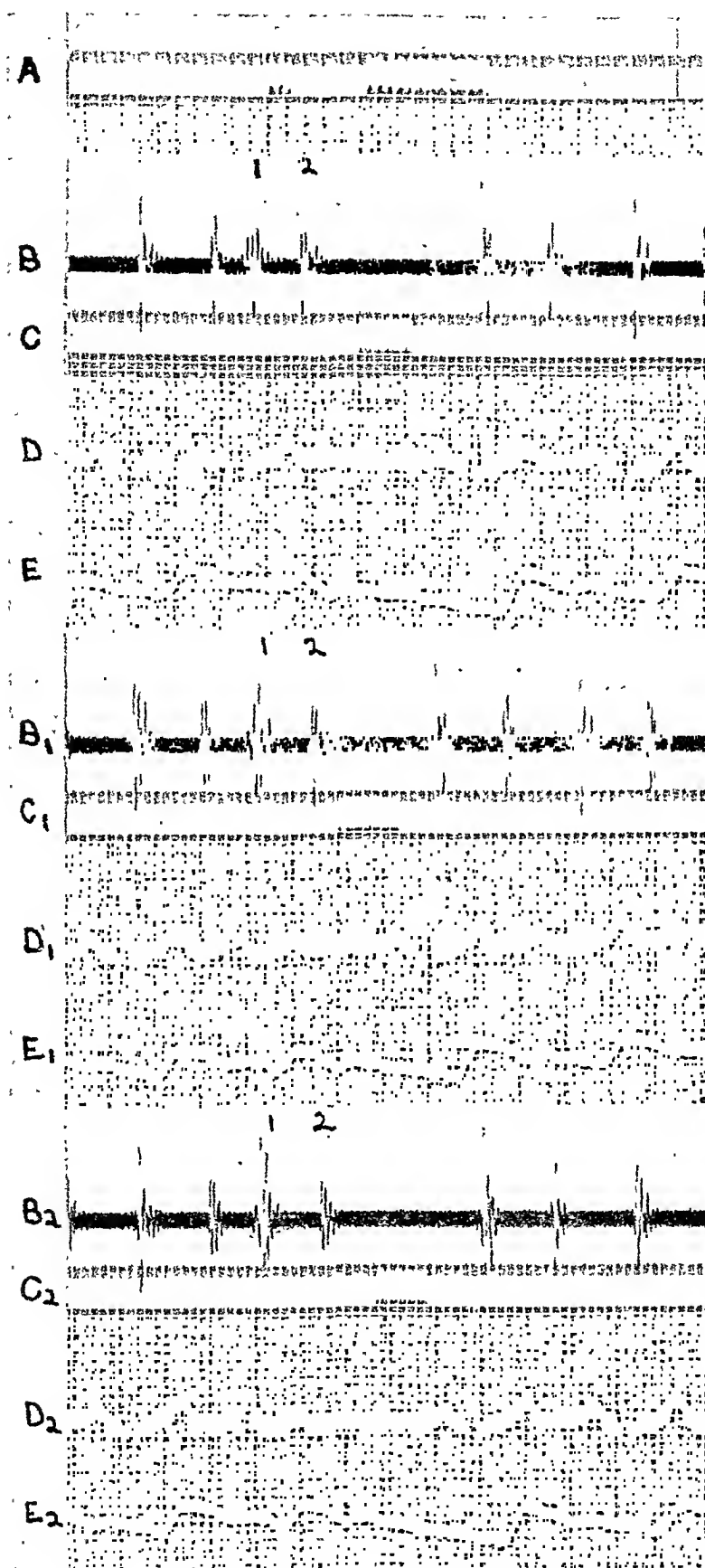


Fig. 4.—G. B. A, Test of reaction time. B, Phonocardiogram. Note that the first sound of the extrasystole is reduced in volume. B₁, In the case of this extrasystole the first sound is of about equal intensity to that of the normal beats. B₂, The first sound of this extrasystole is definitely increased in intensity. C, C₁ and C₂, Signal indicating subject's awareness of extrasystoles. D, D₁ and D₂, Lead II; ventricular extrasystoles. E, E₁ and E₂, Radial pulse tracing.

premature beat. A reaction time 0.20 second (A, Fig. 1), places the time of perception at 0.12 second after the R wave of the extrasystole, and 0.48 second before the next beat would have been due if the rhythm had been uninterrupted.

It is clearly indicated, then that it is the premature beat itself which, by one means or another, is responsible for the symptoms experienced by these individuals. White² mentions as a possible mechanism the simultaneous occurrence of auricular and ventricular systole. This might be a factor in some ventricular premature beats, but it could not explain the identical response of a person whose A-V relationships are normal, as is the case in auricular premature beats (Fig. 2).

Ungerleider and Gubner¹ found that in persons who were conscious of their extrasystoles the first heart sound accompanying these beats was invariably louder than the first sound of the normal beats. This increased intensity is what one would anticipate when systole occurs at a time when the A-V valves are widely separated, particularly since the snapping shut of these valves is responsible for the major component of the first heart sound.³ We, however, could not make such a correlation. For example, Patient A. W. (Fig. 3) was conscious of all but six of the 67 premature beats recorded during the test, yet the accompanying first sounds were never so loud as the first sounds of the normal beats. On the other hand, Patient H. R. (Fig. 1) was conscious of only 20 of the 56 premature beats recorded, yet the first sounds produced by these extrasystoles were always well above normal intensity. In the same individual, variations in volume of the first sounds caused no apparent change in the subjective sensations that these extrasystoles produced. In patient G. B. (Fig. 4) the first sound of the premature beat is of decreased intensity in B , of equal intensity in B_1 , and of increased intensity in B_2 ; yet this patient did not fail to notice any of the 19 premature beats recorded during the test.

Although it is clear that the premature beat is responsible for the symptom of palpitation, no adequate explanation for the mechanism has been found. In some individuals in whom the beats are very premature and are accompanied by loud or unusually prolonged first sounds, it may be that this sound, or the vigorous closing of the widely separated A-V leaflets, causes the disturbance to reach conscious levels. On the other hand, when prematurity is slight, often no more than one sees in a moderate degree of sinus arrhythmia, it is difficult to imagine that the same mechanism is operating. Perhaps in these cases it is the unusual relationship of auricular and ventricular systoles, which sometimes occur simultaneously, that produces the symptoms.

SUMMARY

1. Eleven individuals with extrasystoles and associated subjective sensations were studied in an effort to determine the mechanism responsible for their symptoms.

2. Without exception it was found that the premature beat produced the subjective sensation.

3. In certain instances, when the premature beat occurred during the period of rapid ventricular filling, the symptoms may have resulted from the forceful closing of the A-V valves. In other situations this mechanism does not explain the observations recorded.

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TREATMENT OF CORONARY DISEASE WITH ANGINA BY PERICORONARY NEURECTOMY COMBINED WITH LIGATION OF THE GREAT CARDIAC VEIN

A CASE REPORT

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IT IS well known that in coronary disease sensory disturbances, vasomotor reactions, and mechanical interferences with the coronary blood flow are always intimately interwoven. It is probable that a single group of these pathologic phenomena never acts alone. Surgical operations so far developed for the treatment of coronary artery disease have as their specific objective only the abolition of some reflexes or the correction of some mechanical disturbances of the blood supply to the heart and have not been designed to attack all these abnormal conditions.

No operation which fails to abolish all of these disequilibria can possibly bring about satisfactory and permanent results in the treatment of coronary disease. Operations of such limited scope produce only partial or temporary improvement and do not affect the general aspect or course of the disease. It is no wonder that most of the operations devised have not stood the test of time and are no longer used.

The object of all our experimental studies has been to develop a procedure which would eradicate sensory disturbances, vasomotor reactions, and mechanical circulatory disorders. Because arteriosclerotic disease of the coronary arteries is similar to that of the extremities, it was assumed that surgical methods used in the treatment of peripheral vascular disease could be applied to coronary disease.

Leriche, in 1917, advanced the idea that partial arteriectomy could have value in the treatment of some forms of arteritis. He developed this theory in more detail at the French Surgical Convention in 1922, and has elaborated on it since.¹⁻⁶ In his opinion, the resection of a major diseased arterial trunk interrupts vasoconstrictive pathways and invariably brings about an active vasodilatation. His experimental studies and results seem to substantiate his views. So impressed was he with the beneficial and permanent results of partial arteriectomy in the extremities that he went so far as to suggest it as a worthwhile procedure in coronary disease.

In 1913, Oppel⁷ demonstrated the efficacy of ligating the popliteal vein in the treatment of senile gangrene of the foot. Since then others have confirmed his work. In 1937, Gross, Blum, and Silverman⁸ reported experiments showing

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that occlusion of the coronary sinus in the dog increased the blood supply and reduced the incidence of infarction following ligation of the coronary artery. The author has reported the results of his studies on the effects of both arteriectomy and venous ligation on the dog's heart.⁹⁻¹¹ Partial coronary arteriectomy was found incompatible with life in dogs with normal coronaries. However, when this procedure was combined with coronary venous ligation, the mortality rate was considerably lower. It was concluded that ligation of the great cardiac vein after occlusion of the anterior descending branch of the left coronary artery of the dog helps to maintain adequate coronary circulation after partial coronary arteriectomy. Later, in other experiments (unpublished), a segment of the coronary artery was rendered chronically inflamed. Resection of this modified arterial segment was compatible with life in many instances. Moreover, the incidence of infarction was diminished. Such a procedure has no possible application to clinical cases, as it is impossible to secure coronograms* in man to demonstrate accurately which arterial segment should be resected.

LIGATION OF THE GREAT CORONARY VEIN IN MAN

Although it was realized that coronary venous ligation could do no more than hasten the development of the coronary anastomotic system, the experimental results of coronary venous ligation were so encouraging that it was decided to ligate the great cardiac vein in a carefully selected group of patients in order to determine the value of this surgical procedure for man.

The first patient was operated on in 1939.¹² Since then nine other patients have received the same treatment. A complete study of the final results of their operations was presented before the New England Heart Association in March, 1943. All these patients had a history of coronary thrombosis which was confirmed by electrocardiographic tracings. Some of them gave a history of two attacks of coronary thrombosis. All of them were practically disabled by "angina of effort" and did not respond to rest and medication.

Only one patient died postoperatively. A tear in the pleura occurred while the heart was being exposed. In spite of careful suturing of this tear, the patient died approximately one hour after operation. Pneumothorax under tension was found at autopsy. Nothing else was found to explain the death of the patient.

A 65-year-old patient recovered well from the operation and was discharged from the hospital relieved of his pain. He died from progressive myocardial failure three months after operation. At autopsy the findings were general arteriosclerosis, coronary sclerosis with marked narrowing of the lumen, myocardial fibrosis, and recent infarction of the left kidney. Because this patient had given evidence of cardiac failure preoperatively, he was obviously a poor candidate for coronary venous ligation.

The first patient, operated on in 1939, died suddenly two and one-half years later. Before operation, he was not able to walk one block without developing dyspnea. The slightest emotional upset provoked substantial pain.

*This term applies to the visualization of the coronary arteries by x-ray films.

Five months after operation, he walked five miles without resting and had no discomfort. He resumed his work as a janitor. Frequent examinations up until the time of his death showed that the marked improvement in his condition noticed after venous ligation was maintained. At necropsy there were no adhesions between the pleura and the chest wall. The external surface of the pericardium was smooth and covered by a thick layer of fat reaching the aortic arch and projecting laterally on each side of the heart. The pericardium was slightly thicker than normal. The heart weighed 620 grams. The ramus descendens was occluded 2.5 cm. from its origin and was atheromatous and stenosed throughout its course. The circumflex artery was occluded 5 mm. beyond the bifurcation of the left coronary trunk. The right coronary artery was patent, slightly stenosed, and slightly atheromatous. The left ventricle was dilated;

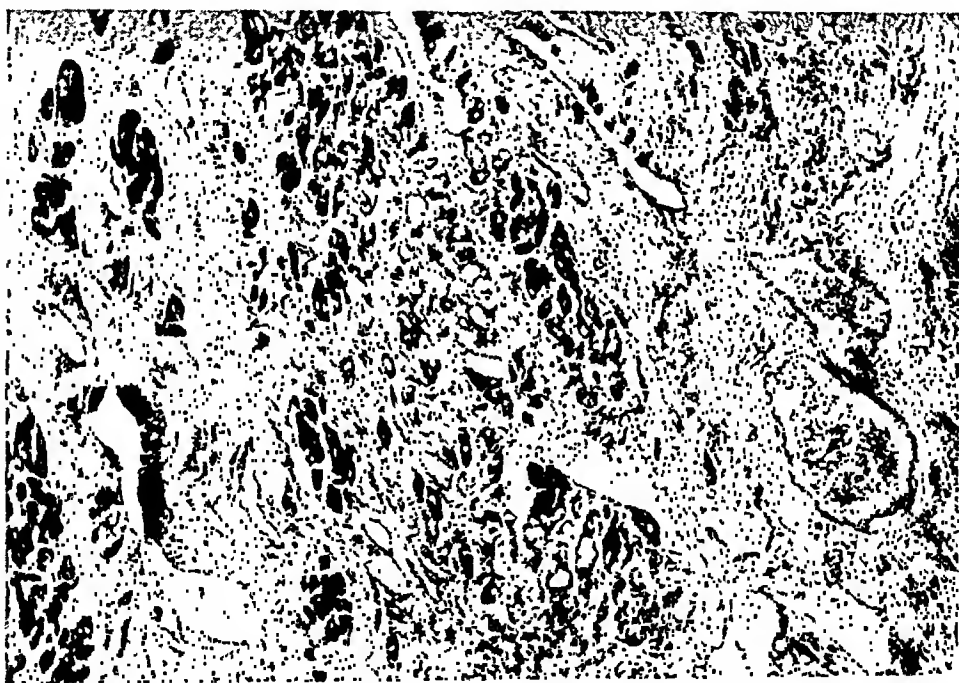


Fig. 1.—Photomicrograph of heart muscle of patient operated on April 19, 1939, showing a high degree of vascularity.

there was no aneurysm. No evidence of old or recent infarction of important size was found. Histologic sections showed a high degree of vascularity of the cardiac muscle. The blood vessels of the posterior and anterior papillary muscles were markedly dilated and gave the appearance of being cavernous. Actual pools of blood were also found in the sections examined (Fig. 1).

Of this series of nine patients, seven are still alive: three of them five years after operation and four of them four years after operation. All seven patients have resumed their work and are able to enjoy life. Although one complained of anginal pain, yet he resumed the occupation which he had had to abandon prior to operation. The others have also returned to the same type of work in which they were engaged before coronary disease incapacitated them and have complained of only slight and infrequent discomfort appearing at the end of a

day's work. Two patients, however, when they are fatigued, have a sensation of pressure without pain over the precordial area.

The experience gained from this small series of cases is of considerable value. The following deductions can be made: (1) The operative mortality was low. The complication which caused death in one patient might have been avoided. (2) The effects of venous ligation on the vascularity of the heart could be carefully studied in the patient who lived over two and one-half years after operation. The histologic sections demonstrated that venous ligation in the heart produces the same results that it does in the extremities. It opens and dilates coronary anastomoses. This anastomotic improvement is not only an immediate and transitory effect but apparently a permanent one. (3) The fact that all the patients who survived were able to resume their work, most of them without discomfort, seems to indicate that coronary venous ligation effects the natural development of collateral circulation and improves both the nutrition of the heart and its functional capacity. This seems about all that one should expect from this surgical procedure.

The coronary nervous system is not modified by this operation. Coronary reflexes, therefore, can still interfere with the function of the heart in different ways; for example, by provoking pain, by producing transitory ischemic myocardial states, and even by contributing to the initiation of ventricular fibrillation and sudden death. These pathologic phenomena were observed to a greater or lesser degree in some of our patients even after operation. It seemed plausible, therefore, that disruption of these reflexes would be beneficial to the patient with coronary disease.

PERICORONARY NEURECTOMY

To abolish or at least diminish substantially the incidence of reflexes resulting from stimulation of the nerve endings of the coronary arteries it was thought feasible to destroy most of the nerve branches reaching or leaving the left and right coronary arteries, since these branches are localized behind the pulmonary artery as well as in the nerve plexus over the ascending aorta. As nerve resection of this sort interrupts sympathetic, vagal, and sensory branches, it was called "pericoronary neurectomy." Experimental studies extending over a period of two years have been carried out by the author¹³ in the Laboratory for Surgical Research at the Harvard Medical School. These studies will soon be reported in detail.

Briefly the results were as follows: In one group of dogs, the circumflex artery was ligated at its origin, that is, approximately 4 to 6 mm. from the aortic opening of the left coronary artery. Twenty per cent of these dogs survived. In the second group, which was prepared in advance by coronary venous ligation, the circumflex artery was ligated at the same level as in the control series. Forty per cent of this group lived. In the third group, prepared in advance by pericoronary neurectomy, ligation of the circumflex was done as in the previous groups. Sixty per cent survived. In the fourth group, prepared in advance by pericoronary neurectomy and coronary venous ligation, the circumflex artery was again ligated as in the previous groups. The survival rate

rose to 86.7 per cent. A fifth group* was prepared by pericoronary neurectomy and coronary venous ligation. Approximately one month after operation, the ramus descendens was occluded while the animals were conscious. Eighty per cent gave no indications of pain; in the remaining 20 per cent the responses were doubtful, but never the typical responses of the control series.

REPORT OF A CASE

These experimental findings suggested that pericoronary neurectomy with ligation of the great cardiac vein would be of greater value in the treatment of coronary disease than venous ligation alone. On Sept. 11, 1944, the first complete denervation of the left coronary artery in man was performed at the Peter Bent Brigham Hospital. Although the final results remain to be seen in this patient, it was thought that a report of this case would be of interest.

The patient, a 45-year-old painter, was admitted to the Surgical Service of the Peter Bent Brigham Hospital on July 27, 1944. One year before admission, he experienced, after exertion, three or four attacks of severe substernal pain which lasted three to four minutes each. He had no further trouble until three and one-half months before admission, when he noticed that walking uphill for a few minutes would bring on an attack of severe, aching substernal pain which radiated to the back and was accompanied by a sensation of numbness in the left upper arm. The pain came on suddenly and was relieved by rest. Frequently the attacks of pain were accompanied by nausea, but he never vomited. Such an attack never occurred while he was at rest.

An electrocardiogram was taken on June 19, 1944, in the Outpatient Department of the Peter Bent Brigham Hospital. It was reported to show left axis deviation and an abnormal Lead IV. A 7-foot heart film showed the heart to be only 4 per cent above normal in size. Fluoroscopy showed nothing remarkable. The physical examination was negative. A diagnosis of coronary disease and angina pectoris was made. Nitroglycerin was prescribed and gave some relief. One week before admission, the patient experienced an attack of pain which was similar to the previous attacks except that it occurred while he was resting in bed. He sat up in bed all night, as that seemed the only position in which he could tolerate the pain. He had no difficulty in breathing. The pain persisted for the next two days and was so severe that he could not rest. On the third day the pain disappeared. During his hospitalization he had several more brief attacks of substernal pain. These attacks occurred both at rest and after meals.

On examination, the patient was found to be a well-developed, rather thick-set man whose nutrition was good. Apart from the cardiovascular system, the results of the examination were essentially negative. On admission, the temperature was 99.2° F.; the pulse, 104; and the respirations, 18. The white count was 8,400, and the blood pressure was 120/80. The apex impulse was neither seen nor felt. By percussion the left border of cardiac dullness was found at the midclavicular line and the right border 4.5 cm. from the midsternal line.

*Report to be published by Drs. Orvar Swenson and Merle Fauteux.

Heart sounds were distant and a faint apical systolic murmur was present. The rhythm was regular.

Dr. Samuel A. Levine examined the patient and concluded that he had had a coronary thrombosis ten days before admission to the hospital. He advised bed rest, observation for six weeks, and re-evaluation after that period of time.

An electrocardiogram taken on July 28, 1944, showed left axis deviation, diphasic T waves in Lead I, and a normal Lead IV. The heart rate was 63 per minute; the P-R intervals were 0.16 second; and the QRS complexes were 0.08 second in duration (Fig. 2). The patient was kept in bed. He had only occasional attacks of angina and these gradually disappeared. On Aug. 14, 1944, he was allowed to leave his bed for the first time. Walking around the ward did not seem to trouble him. On Aug. 21, 1944, a two-stair exercise tolerance test performed by Dr. J. E. F. Riseman showed that 28 trips could be made before pain was initiated.

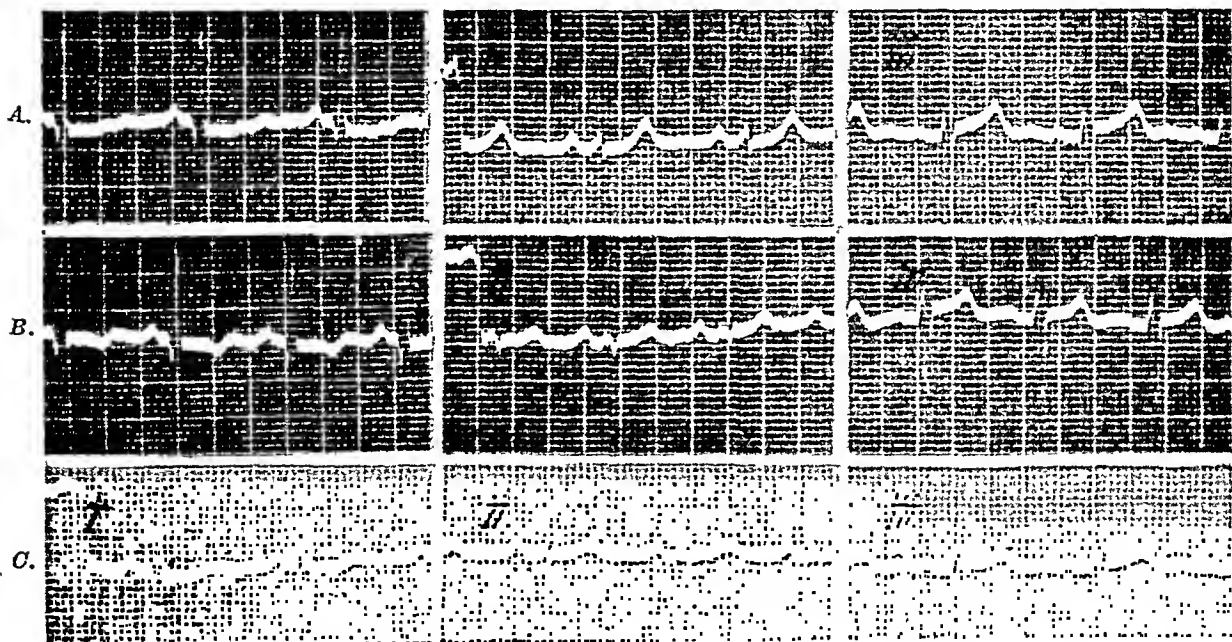


Fig. 2.—Electrocardiograms made before operation: A, July 28, 1944; B, Aug. 17, 1944; C, Aug. 28, 1944. Somewhat inverted T waves in Lead I and left axis deviation.

An electrocardiogram taken on Aug. 28, 1944, showed a normal Lead IV, a rate of 79 per minute; P-R intervals of 0.12 second; and QRS complexes of 0.08 second in duration (Fig. 2). The circulation time varied from 37 to 12 seconds. The vital capacity was 3,500 cubic centimeters.

On Sept. 11, 1944, pericoronary neurectomy combined with ligation of the great cardiac vein was performed under ether anesthesia with the assistance of Drs. Orvar Swenson and Charles A. Hufnagel. No special preoperative medication was administered. A right-angle incision was made, beginning at the level of the second left rib, curving over the right side of the midsternum and then going straight down approximately to the xiphoid. The second, third, and fourth left ribs as well as part of the sternum at this level were partially

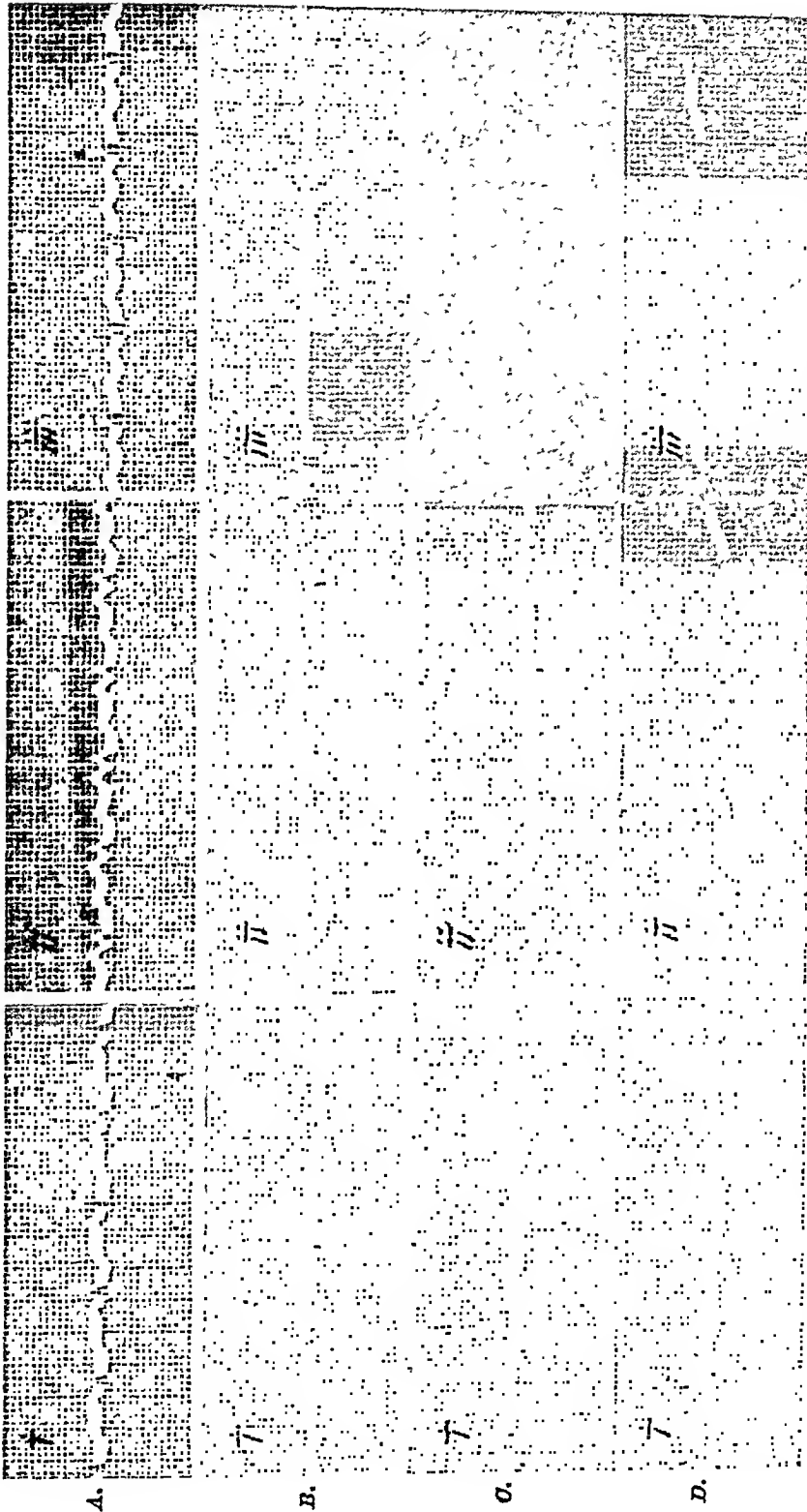


Fig. 3.—Electrocardiograms made at the time of operation. A was made after anesthetization but before incision. It is essentially the same as in Fig. 2. B was made during temporary venous occlusion. T₁ is slightly upright. C was made during pericoronary neurectomy. Lead I shows artifacts probably from manipulations. Lead II shows arrhythmia due to shifting pacemaker in A-V node. Lead III was not taken. D was made after phenolization. Artifacts appear in Lead I. Leads II and III show arrhythmia.

resected. With blunt gauze dissection, the pleura and left lung were gradually pushed laterally so as to give access to the cardiac area. The pericardium was incised vertically and then transversally. After exposure of the heart, the great cardiac vein was freed just below the origin of the coronary sinus. A ligature was passed under the vein, and both ends of the thread were crossed temporarily in order to observe the effects of coronary venous occlusion on the heart. Since this procedure did not produce any abnormalities in the blood pressure, pulse rate, or electrocardiogram (Fig. 3, *B*), the level of obstruction was considered satisfactory. The vein was not tied immediately because this would have caused troublesome distention of small venules in the field of the pericoronary neurectomy.

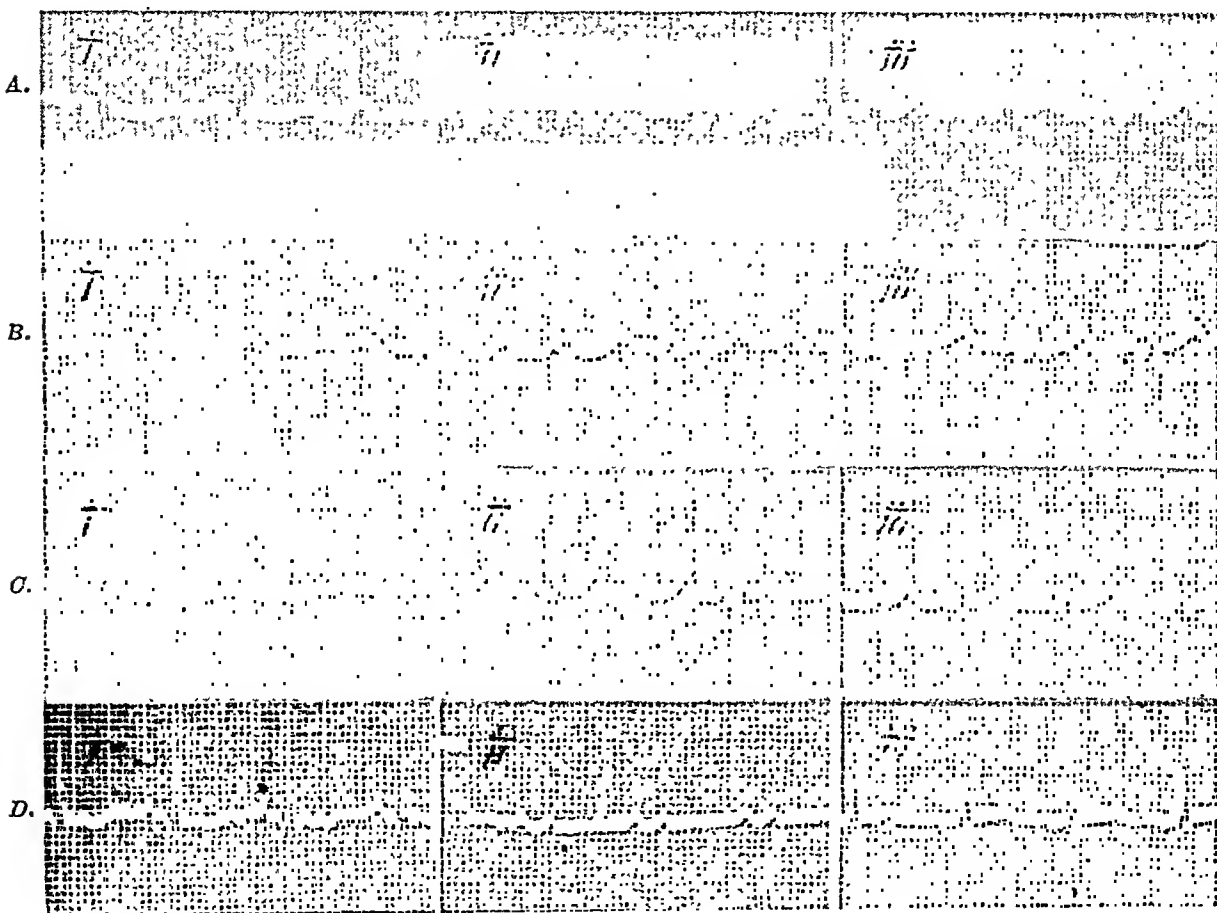


Fig. 4.—Electrocardiograms made after operation: *A*, immediately after operation; *B*, one hour and twenty minutes after operation; *C*, twenty-four hours after operation; and *D*, thirty-six days after operation.

The pulmonary artery was freed from the aorta and reflected to the right to expose the origin of the left coronary artery and the plexus between the aorta and pulmonary artery. The epicardial tissue over the left coronary artery was incised and resected down to a few millimeters below the bifurcation of the main trunk. Nerves emerging from behind the pulmonary artery and coursing toward either the main trunk of the left coronary artery or the ramus descendens were exposed and resected. Likewise the nerve branches merging from the left side of the aorta and reaching the left coronary main trunk or the origin of the circumflex branch were exposed and resected. During this procedure, the areas

exposed were frequently touched with small pieces of cotton soaked in novocain solution (2 per cent). Then the left coronary main trunk and the proximal part of both circumflex and ramus descendens branches were phenolized. During all these maneuvers, the heart behaved normally. There was hemorrhage, except for an insignificant oozing from the fat tissues covering the artery which was rapidly and easily controlled by application of fibrin foam. The electrocardiographic changes during operation were neither marked nor important (Fig. 3). A shifting pacemaker with the impulse starting sometimes high up, and sometimes low down in the A-V node which occurred during the dissection of the vein (Fig. 3, C); occasional ventricular extrasystoles at the beginning of the operation on the heart; bradycardia after ligation of the great cardiac vein. It should be stressed that the tracings obtained during and after dissection of perivascular nerve endings do not show significant changes in the T waves or in the S-T intervals.

The great cardiac vein was ligated. The pericardium was not sutured. The chest wound was closed without drainage. At the end of the operation, the patient was doing well (Fig. 4).

Postoperative Course.—Immediately after operation, oxygen was administered continuously for approximately four hours and then discontinued. Two days after operation, the patient was sitting up in a chair. On September 17, stitches were removed. The wound was normal. The patient progressed well until September 20, when he complained of tenderness of the calf of the left leg. He had a positive Homans' sign (pain in the calf on forced dorsiflexion of the foot). It was believed that the patient had thrombophlebitis. Bilateral femoral vein ligation under local anesthesia was performed by Dr. Orvar Swenson. A marked rise in temperature which later occurred subsided within twenty-four hours after the cessation of sulfadiazine therapy. The patient was discharged from the hospital on Oct. 4, 1944.

Since his discharge, he has been seen at frequent intervals. He never complains of anginal pains, either at rest, after meals, or after exercise. On Oct. 27, 1944, he developed a pleuropulmonary infection on the right side which subsided rapidly after treatment. Exercise tolerance tests were carried out on and following Dec. 5, 1944, by Dr. J. E. F. Riseman. After twenty-eight trips on the two-stair apparatus, he did not develop pain. The electrocardiograms taken after exercise were quite similar to the postexercise tracings taken before surgery. At that time the tracing showed only minimal S-T depression.

The patient has been seen recently and states that he is much improved, has no more pain, and has resumed his work.

SUMMARY

A case of coronary disease with angina has been reported. Pericoronary neurectomy combined with ligation of the great cardiac vein was carried out six months ago. Since the operation the patient has shown much improvement, has had no pain, and has been able to work.

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PAROXYSMAL PULMONARY EDEMA CONSEQUENT TO STIMULATION OF CARDIOVASCULAR RECEPTORS

I. EFFECT OF INTRA-ARTERIAL AND INTRAVENOUS INFUSIONS

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THE pathogenesis¹ and treatment² of paroxysmal pulmonary edema were recently reviewed by one of us (A. A. L.), and it was pointed out that there are two conflicting theories as to the pathogenesis. The first explains the syndrome as the effect of sudden failure of the left ventricle with a normally functioning right ventricle.³⁻⁶ The other theory attributes the edema to a sudden increase in the permeability of the lung capillaries caused by nerve reflexes.⁷⁻⁹

In previous attempts to produce acute pulmonary edema similar to that seen in hypertensive patients, the following experimental devices have been used: (a) massive injection of adrenalin (in rabbits)¹⁰⁻¹⁴; (b) ligature of the aortic arch and of some of its efferent arteries (in rabbits or dogs)^{3, 15-17}; and (c) massive intravenous infusion of saline solution (in rabbits, cats, and dogs).

Slow infusion of saline into the veins of the dog can be continued for hours, until enormous amounts have been introduced, without producing any symptoms, as Wiggers¹⁸ has shown. Therefore, various authors¹⁹⁻²¹ have resorted to the device of cutting the yagi before the infusion in order to produce edema.

Rapid intravenous infusion of even an enormous quantity of fluid, amounting to three times the blood volume, given in less than thirty minutes, only irregularly produces edema of the lungs. It has been found, however, that the rapid *intracarotid* infusion of saline solution produces pulmonary edema more consistently.^{24, 25}

The technique and preliminary results have been described elsewhere.²⁵

METHODS

Mongrel dogs weighing 5 to 20 kg. were used. Smaller dogs and pregnant bitches were found to be unsuitable. Anesthesia was induced by the subcutaneous injection of 3 mg. of morphine sulfate per kilogram of body weight. This was followed twenty minutes later by 1 Gm. per kilogram of body weight of urethane given by stomach tube. Occasionally, a small additional amount of urethane was required. The choice of anesthesia is important, since sedatives and anesthetics may inhibit experimental pulmonary edema.^{12, 17, 20, 26} In early experiments we used chloralose, but when this drug became unobtainable we resorted to the use of urethane, which we found almost as satisfactory since it has no action on cardiovascular receptors.^{26, 27}

From the Surgical Research Laboratory of the Beth Israel Hospital, Boston, Massachusetts. This paper was read before the New York Cardiological Society, Oct. 25, 1944.
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Infusion.—Arterial infusions into the carotid and the femoral arteries were given with the cannulae directed toward the periphery (head, legs); venous infusions were given with the cannulae directed centrally. Large amounts of isotonic saline solution, Tyrode's solution, bovine albumin-salt solution, and blood were administered separately under high pressure. Arterial infusions were given under a pressure of 280 to 300 mm. Hg and venous infusions under a pressure of 50 to 150.

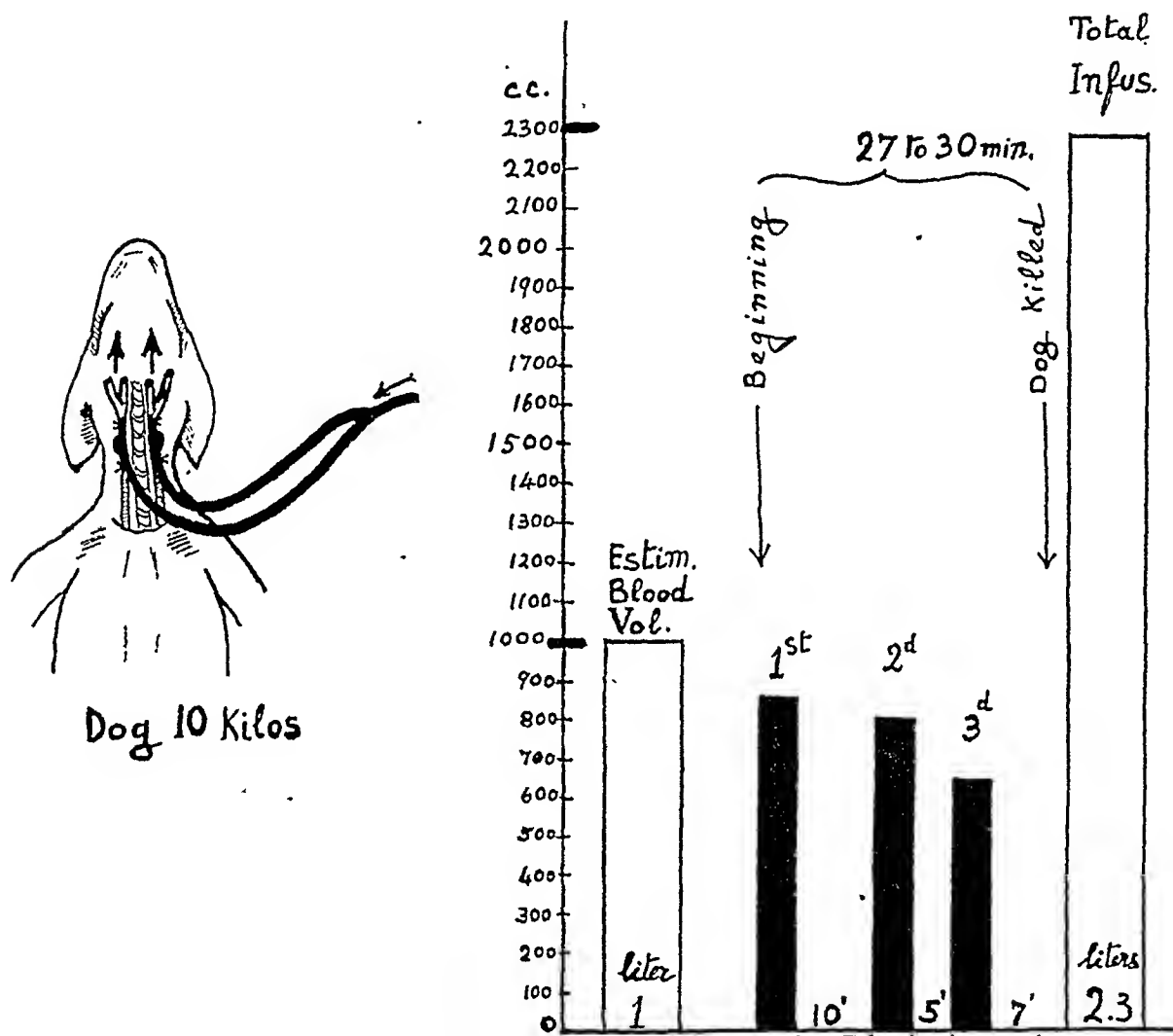


Fig. 1.—Sketch of the method for interrupted infusion.

In the first series of experiments uninterrupted infusion of fluid was continued until the death of the dog. In a second series it was thought preferable to alternate periods of infusion with periods of rest in order to avoid anoxemia of the brain, to permit the development of the edema, and to limit the total amount of fluid used.

The total quantity of injected fluid usually amounted to 2.3 times the animal's estimated blood volume. The blood volume was estimated to be 10 per cent of the animal's total weight. The total volume of infused fluid was occasionally varied for different purposes. The initial infusion was 85 per cent of the animal's estimated blood volume and was administered in from one to two

and one-half minutes depending on the size of the dog. Ten minutes after starting the first infusion another infusion amounting to 80 per cent of the original blood volume was given. Five minutes after the end of the second infusion 65 per cent of the original blood volume was infused and required a correspondingly shorter period of time. If the animal survived this procedure, it was sacrificed seven minutes after the end of the last infusion. The trachea was clamped, the inferior vena cava was cut, the heart was severed from its connections, and the lungs were removed within two to three minutes.

The fluid to be infused was contained in a large bottle. The pressure in the air chamber of the bottle was controlled by means of a pump and was measured with an aneroid manometer. The fluid escaped through a rubber tube and entered the two glass cannulae connected to the two common carotid arteries. The proximal ends of the vessels were tied at the beginning of the experiment and were left so until the end. Because of the ligation of the common carotids, the artificially high pressure present in the carotid arteries during the short periods of infusions was followed by longer periods of low carotid pressure.

Evaluation of the Edema.—In some of the first experiments we tried to detect pulmonary edema by physical examination. This proved to be unsatisfactory. All animals developed dyspnea during the experiment. This was nearly always accompanied by bronchospastic phenomena and either dry, whistling, or crackling noises were audible upon auscultation. Moist râles were difficult to recognize because of the other auscultatory findings. Pink froth coming out of the nose unmistakably indicated the existence of edema. However, the tremendous hypertension in the head may lead to salivation and occasionally bleeding from the gums and nose. This may result in confusing gurgling sounds which are not due to pulmonary edema. Vomiting sometimes occurs.

In other experiments we tried to detect the presence of edema by opening the trachea and observing the spontaneous outpouring of frothy sputum. This also proved deceptive; in some experiments moderate edema gave rise to early outpouring of frothy material; in others, severe edema did not. Therefore, we decided that only data based on post-mortem findings were to be relied upon in determining the presence and degree of pulmonary edema.

The gross appearance of the lungs and the presence of foam in the trachea were noted. The trachea was clamped and cut 2 inches above the carina, and the lungs were weighed without any loss of fluid from the trachea. The lungs were then inverted and squeezed firmly in order to note the character and amount of fluid and foam which they contained. Section of the parenchyma likewise yielded information as to the amount of edema present in different lobes.

The normal weight of the lungs of animals sacrificed during other experiments was studied in early spring and in midsummer. By dividing the weight of the lungs in grams by the weight of the dogs in kilograms, we obtained an index representing the relative weight of the normal lungs, including a normal amount of blood. This is referred to as the *lung/body index*.

In early spring, when the temperature was still low, this index was found to vary between 0.75 and 1.05 and averaged 0.86.* In summer, when the temperature was high, the index was from 1.13 to 1.66 and averaged 1.33. Therefore, an index of 0.8 to 1.2 in winter and early spring and an index of 1.3 to 1.5 in summer may be considered a normal index for dogs given large amounts of fluid.

Fluids Used.—Four different types of fluid were employed: (a) Tyrode's solution; (b) physiologic salt solution; (c) a 5 per cent bovine albumin solution in normal saline†; and (d) oxygenated dog blood. All fluids were injected at 37° C. When the injections were repeated at room temperature the results were the same. Fine, Seligman, and Frank²⁸ have demonstrated that dogs tolerate bovine albumin. Dog blood obtained by bleeding two heparinized dogs before the beginning of the experiment was kept for about an hour at 37° C. and shaken before use in order to saturate the red cells with oxygen.

Tracings and Evaluations.—Venous pressure was determined by the Kennedy-Lyon-Burwell technique. Arterial pressure was determined by direct femoral puncture or cannulation. Heparin was used in the latter instance. In some animals kymographic tracings were made. Electrocardiographic and phonocardiographic records, as well as roentgenograms of the chest, were obtained in several experiments. By considering gross observations together with the lung weights we graded the edema from 1 to 4. The procedure employed is indicated in Table I.

TABLE I. FINDINGS USED IN GRADING THE DEGREE OF PULMONARY EDEMA

INDEX LUNG/BODY	FOAM	EDEMA
1.20-1.60	None	- (congestion)
1.40-2	Slight	+
1.40-2	Abundant	++
1.60-2.75	Fair amount	++
1.60-2.75	Abundant	+++
2.75-5 (or above)	Abundant	++++

TABLE II. CONTINUOUS INFUSION INTO CAROTID ARTERIES

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COM- PARED TO ESTIMATED NORMAL BLOOD VOLUME	INDEX LUNG/ BODY	GRADE OF EDEMA	ANESTHESIA	MODE OF DEATH
SA	20	About 3	-	++	Chloralose	Spontaneous
9A	24	About 3	-	++++	Chloralose	Spontaneous
11A	19	1	-	+	Chloralose	Spontaneous
13A	27	3	-	+++	Chloralose	Spontaneous
17	7.4	2.5	3.37	++++	Urethane	Spontaneous
44	12.7	1.5	1.96	+	Urethane	Dog killed

*In a study on the weight of the lungs of normal dogs, Wood and Moe²¹ obtained an index of 0.8, with a minimum of 0.54 and a maximum of 0.97. Since these dogs were killed by bleeding, the lungs had a subnormal content of blood and, therefore, a lower weight.

†This was provided by the Armour and Company, Chicago, Ill., through the courtesy of Prof. E. J. Cohn, Department of Physical Chemistry, Harvard Medical School.

RESULTS

Continuous Carotid Infusions.—Continuous infusion of saline was used in six experiments. The external and internal carotid arteries and some of the small branches were ligated in five of them, so that the fluid entered the animal only through the small vessels originating immediately above the carotid sinus. Death of the dogs occurred after amounts of fluid varying from one to three times the blood volume had been injected (Table II).

Standard Interrupted Carotid Infusion.—Infusions given in three interrupted periods sometimes caused the death of the animal. The first infusion generally produced slight dyspnea; the second was accompanied and followed by severe dyspnea; and the third was followed by extreme dyspnea, then apnea and death. Pink froth often poured from the nostrils between the second and third infusions or during the latter (Table III).

Infusion with *Tyrode's solution* produced far less severe dyspnea than infusion with saline: dyspnea was entirely absent in one experiment (Table IV). Infusion with *bovine albumin-salt solution* resulted in dyspnea comparable to

TABLE III. STANDARD INTERRUPTED INFUSION INTO THE CAROTID ARTERIES WITH PHYSIOLOGIC SALT SOLUTION

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COM- PARED TO ESTIMATED NORMAL BLOOD VOLUME	INDEX LUNG/ BODY	GRADE OF EDEMA	MODE OF DEATH	REMARKS
27	7.7	2.5	1.89	++	Dog killed	-
31	8.6	2.8	2.44	+++	Dog killed	-
46	9	2.5	4.44	++++	Dog killed	-
50	6.4	2.4	2.74	+++	Dog killed	Tracheotomy
58	10.4	2.3	2.75	+++	Dog killed	-
64	9.6	2.3	1.69	++	Dog killed	Ligature of jugular veins
80	13.4	2.5	1.86	+++	Dog killed	-
89	8	2.3	5.40	++++	Dog killed	Tracheotomy
92	13	2.3	2.69	+++	Spontaneous death	-
102	19	2.3	5.26	++++	Spontaneous death	-

TABLE IV. STANDARD INTERRUPTED INFUSION INTO THE CAROTID ARTERIES WITH DIFFERENT FLUIDS

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COM- PARED TO ESTIMATED NORMAL BLOOD VOLUME	INDEX LUNG/ BODY	GRADE OF EDEMA	MODE OF DEATH	FLUID
1	11.2	3	-	+++	Spontaneous	Tyrode's
56	8.2	2.3	1.56	+	Dog killed	Tyrode's
59	5.7	2.5	1.36	-	Dog killed	Tyrode's
60	5	2.5	2.56	++	Dog killed	Tyrode's
61	15.9	2.3	2.78	+++	Dog killed	Tyrode's
5	13.4	2	5.22	++++	Spontaneous	Bovine albumin- salt solution
34	9.8	1.9	2.29	+++	Spontaneous	Bovine albumin- salt solution
55	7.2	2.3	4.72	++++	Dog killed	Blood

that caused by saline solution. It also produced severe edema (Table IV). Infusion with *blood* caused only moderate dyspnea but very severe edema (Table IV).

Infusion made into only one carotid artery produced moderate pulmonary edema.

Infusion Into Other Vessels.—Infusion was made into the femoral arteries of five animals in a manner similar to that used for the standard infusion into the carotids, except that two and one-half to three times the estimated blood volume was introduced. Three out of five dogs had perfectly dry lungs, one had moderate pulmonary edema, and one had severe pulmonary edema (Table V).

TABLE V. STANDARD INFUSION INTO THE FEMORAL ARTERIES

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COM- PARED TO ESTIMATED BLOOD VOLUME	INDEX LUNG/ BODY	GRADE OF EDEMA	MODE OF DEATH	FLUID	REMARKS
2	12.2	2.9	0.9	-	Dog killed	Tyrodé's	--
78	5.3	3	1.26	-	Dog killed	Saline	
81	11.4	3	2.45	+ + +	Dog killed	Saline	Summer
84	5.2	2.5	1.58	+	Dog killed	Saline	Summer
90	7.8	2.5	1.18	-	Dog killed	Saline	--
38	12.5	2.4	1.64	+	Dog killed	Saline	Infusion to- ward the center

Infusions into veins were made under pressure of from 50 to 150 mm. of mercury. In one experiment the jugular veins were used, with the fluid injected toward the heart. In all others the femoral veins were used, with the fluid also directed toward the heart. Severe pulmonary edema occurred in only two out of eight dogs, while minimal edema developed in one (Table VI).

TABLE VI. STANDARD INFUSION INTO VEINS

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF FLUID AS COM- PARED TO ESTIMATED BLOOD VOLUME	INDEX LUNG/ BODY	GRADE OF EDEMA	MODE OF DEATH	PRESSURE (MM. HG)	REMARKS
3	14	2.7	-	-	Dog killed	50	Absolutely dry lungs. 1 fem- oral vein
11	17	1.7	1.05	-	Dog killed	100-120	1 femoral vein
51	10	3	1.25	-	Dog killed	110-120	Jugular veins
65	10	3	4.05	+++	Dog killed	140-160	Femoral veins
67	9.3	2.3	1.35	-	Dog killed	110-120	Femoral veins
68	10.9	3	1.46	+	Dog killed	120	Femoral veins
83	7.8	2.3	1.31	-	Dog killed	100	Femoral veins
91	10.9	2.3	3.94	++++	Dog killed	100	Femoral veins —summer

Effect of Infusion Upon Arterial and Venous Pressure.—Femoral arterial pressure was measured in two standard experiments and recorded graphically in a third. After occlusion of the common carotid arteries the blood pressure rose to 170 to 190, but returned to normal levels during the first infusion. The same alternation of high and normal blood pressure was repeated during the second infu-

sion, but there was a gradual tendency for the blood pressure to rise. After the end of the third infusion the systolic pressure was higher than at any previous time, though not markedly so; it reached 170 mm. Hg in two experiments and 160 mm. Hg in another.

Femoral venous pressure was measured in four experiments. From a normal figure of 3 to 7 cm. of water the pressure rose to 50 to 70 at the end of the first infusion, but returned to normal within five to eight minutes. It rose to 75 to 85 at the end of the second infusion and fell to 20 to 35 at the end of the rest period. It reached 95 to 100 at the end of the third infusion, and dropped later to 15 to 30 just before the animals were sacrificed.

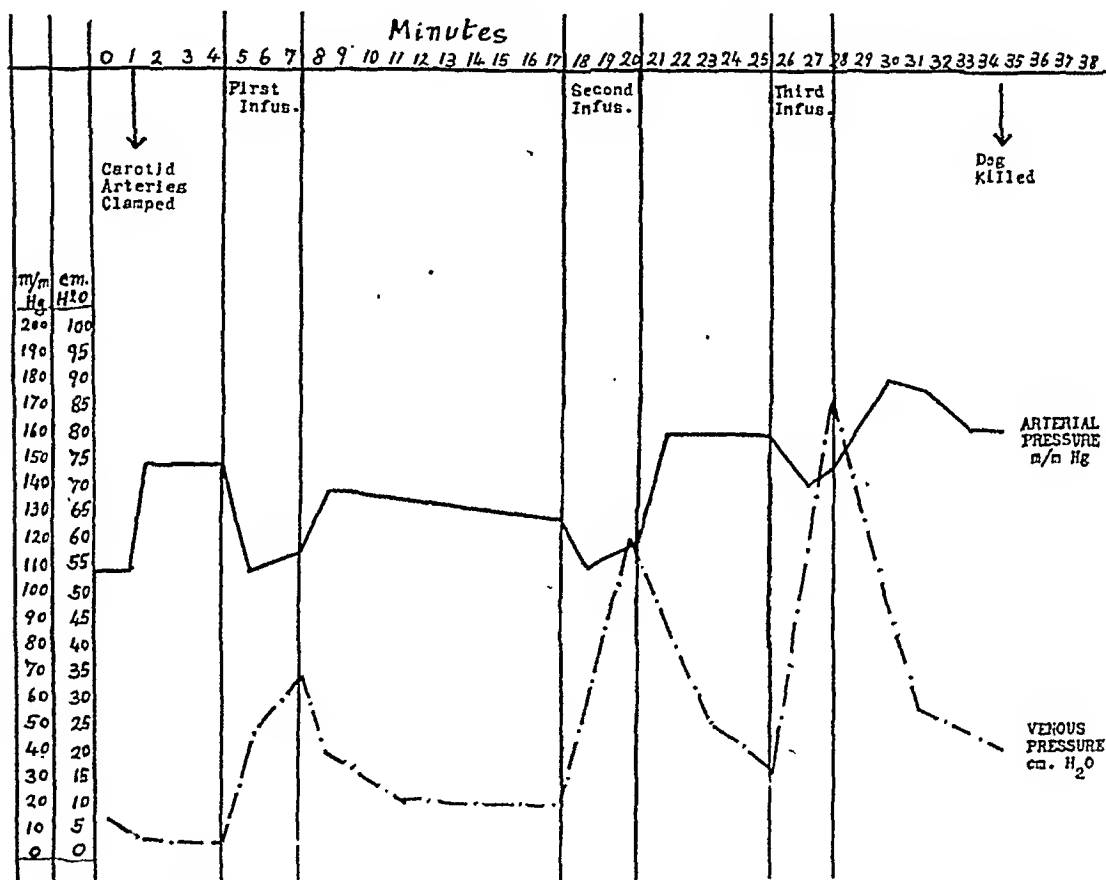


Fig. 2.—Changes of the venous and arterial pressures during the standard infusion of one dog.

Electro- and Phonocardiograms.—These graphic studies were recorded in two experiments. Cannulation accelerated the heart rate from an average of 115 per minute to an average of 140. The heart rate reached 180 after the first infusion but rose no higher after subsequent infusions. Sinus rhythm was maintained. All waves in the electrocardiogram became smaller, and either inversion or flattening of the T waves developed.

The phonocardiogram showed signs of myocardial strain, such as gallop rhythm or diastolic rumble, and a terminal decreased amplitude of the second sound. A functional systolic murmur was observed in one experiment.

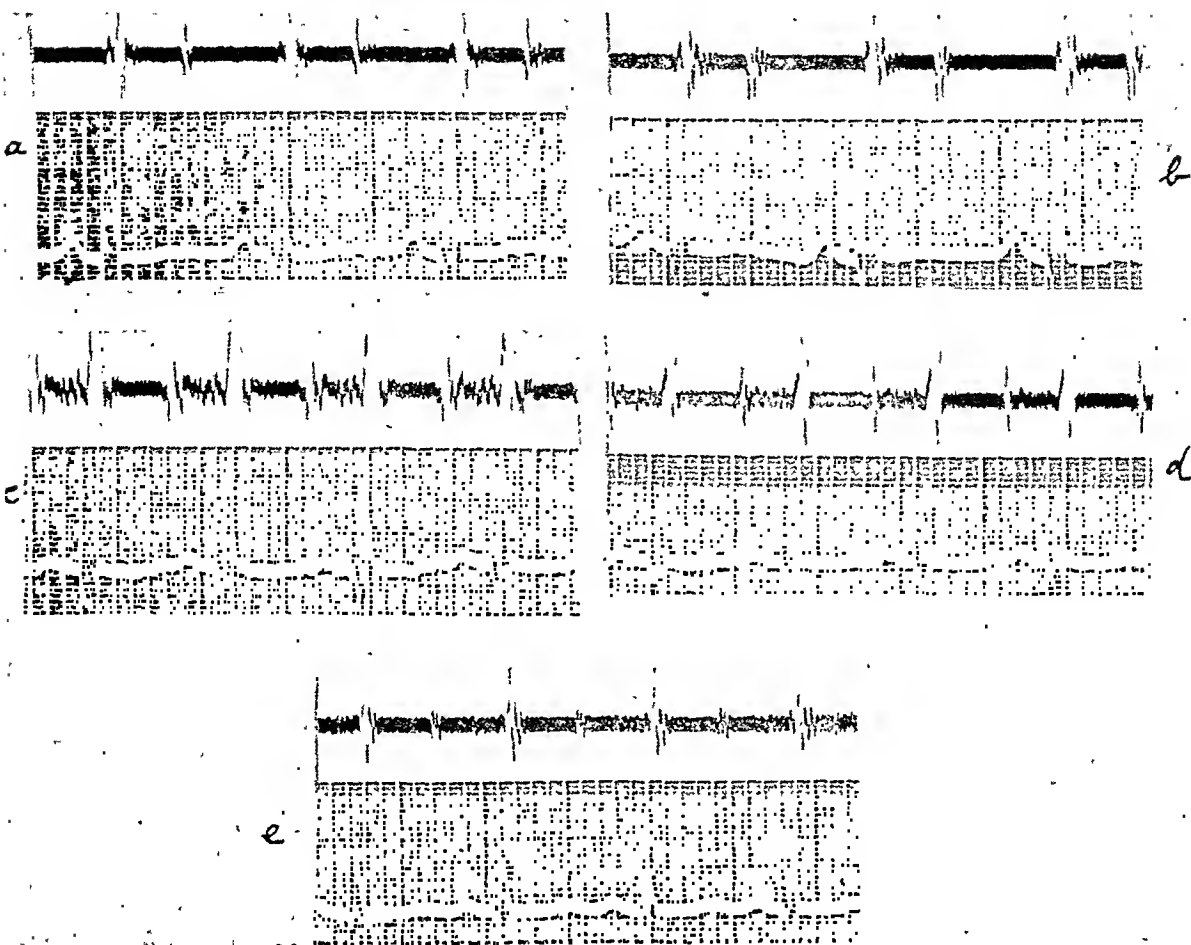
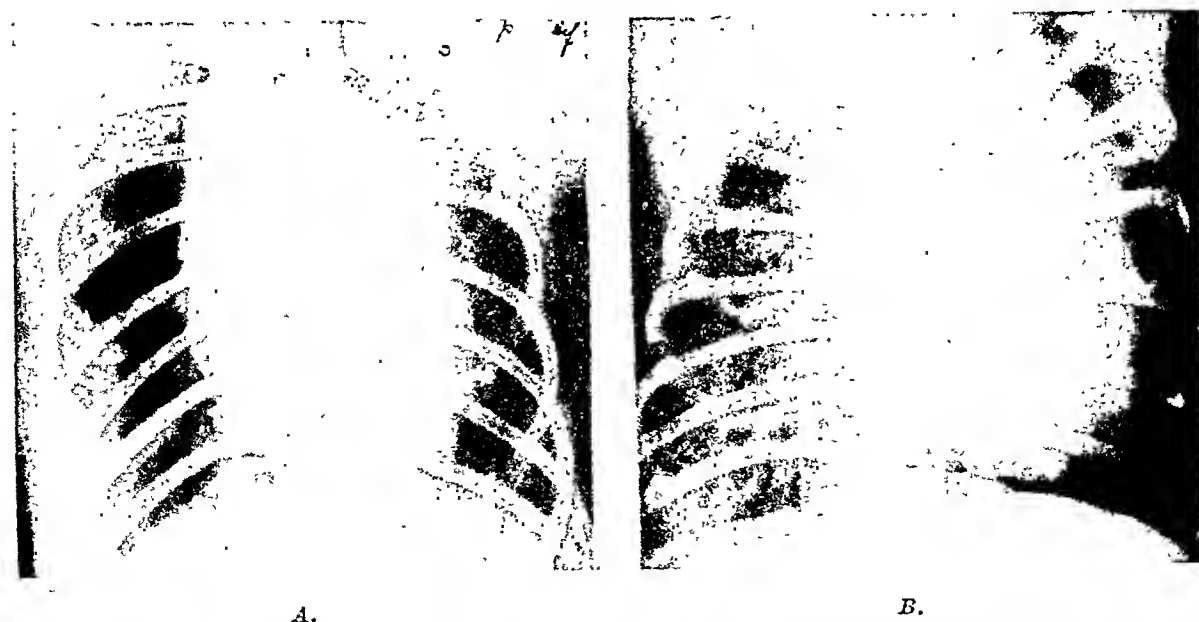


Fig. 3.—Electro- and phonocardiogram of a dog during the standard infusion: *A*, before cannulation of the carotids; *B*, after cannulation; *C*, after the first infusion; *D*, after the second infusion; and *E*, after the third infusion, immediately before death.



A.

B.

Fig. 4.—X-ray of the thorax of a dog: *A*, before any infusion; and *B*, after the third infusion. Remarkable enlargement of the heart and of the chest. Haziness of the lung fields.

Roentgenograms.—Films of the thorax were taken in three experiments with the animal lying flat on the back. The condition of the heart and lungs was studied and compared before cannulation, after the second infusion, and after the third. The tremendous increase in the blood volume and the storage of fluid in the blood reservoirs made the comparison difficult because the thorax was apparently increased in size. This was the result (a) of increased size of the heart; (b) of increased size of the abdominal organs; and (c) of vascular distention, edema, and compensatory emphysema of the lungs. All these factors caused widening of the intercostal spaces. The edema was indicated by the haziness of the lung fields.

Post-Mortem Findings.—Fluid was present in the abdominal cavity. The urinary bladder was distended and the small bowel contained fluid. However, very little or no fluid was present in the pleural and pericardial cavities. Both the liver and the spleen were distended and cyanotic. Cyanosis of the abdominal organs was remarkable. The stomach was tremendously distended both by fluid and by gas. The heart was uniformly enlarged but not flabby. The lungs were distended and showed red patches separated by pale areas. Whitish or pink foam poured from the cut trachea, and from the parenchyma a red bubbling froth flowed which was increased by squeezing.

DISCUSSION

This study was made in order to re-evaluate earlier experiments²⁴ bearing on the possibility of producing pulmonary edema by the perfusion of the isolated head. We were able to demonstrate that in those earlier experiments fluid escaped from the head into the trunk through venous channels. This led to the present systematic study of (a) infusion into various vessels, (b) infusion into the carotid arteries with unimpaired venous return to the heart, and (c) infusion into the carotid arteries by means of a new technique.

Paroxysmal pulmonary edema, caused by the rapid infusion of fluid under high pressure into the carotid arteries, is only one aspect of a complex picture of transudation into serous cavities and into the lumen of various organs, such as the bronchial tree and the gastrointestinal tract. However, there is no definite connection between the amount, or even the existence, of pulmonary edema and the degree of transudation elsewhere. As a matter of fact, experiments with rapid infusion into veins often caused a remarkable degree of ascites without the production of any pulmonary edema. Moreover, the pulmonary edema produced by carotid infusion may be prevented by various procedures to be described, without changing the volume of the ascites, of the transudation into the gastrointestinal tract, or of the salivation. This shows that pulmonary edema is a particular aspect of the picture, and that the rapid increase of the blood volume is only one of the factors leading to transudation into the alveoli. Experiments with infusion into other vessels confirm this conclusion. If we exclude the experiment of infusion into the femoral arteries toward the heart, which may be explained in a different way, we obtain the following results: (a) In thirteen experiments with infusion either into veins or into femoral ar-

teries, where the average amount of infused fluid was 2.57 times the blood volume, pulmonary edema was found in 27.7 per cent of the dogs. (b) In eighteen experiments with infusion into the carotid arteries, where the average amount of infused fluid was 2.38 times the blood volume, pulmonary edema was found in 89 per cent of the dogs. This shows that *the amount of fluid plays only a secondary role* and that *the route of infusion is of primary importance*.

Viscosity of the fluid seems to act in an inverse way; the more viscid the fluid the greater the edema. Obviously, when the infused fluid has a low viscosity it is excreted, secreted, and stored with such speed that the venous return to the heart is relatively less than when it has a high viscosity. This factor is more important than ability of the fluid to penetrate the walls of the lung capillaries, and accounts for lower grades of pulmonary edema with Tyrode's solution and saline than with albumin or blood. This conclusion is in agreement with that of Yeomans, Porter, and Swank.²³

The chemical composition of the fluid is of some importance. When either Tyrode's solution or blood is substituted for plain saline, the dyspnea is very much less severe. This can be attributed to the presence of calcium and potassium ions, and in the latter case to the presence of oxygen. The absence of these substances is likely to effect the receptors of the carotid body and the brain centers. The effect on the lung capillaries is considerably less, since the fluid is mixed with blood before reaching them. However, in spite of this fact, pulmonary edema may occur with either Tyrode's solution or blood.

Asphyxia is not likely to occur because of the shortness of the periods of infusion. Moreover, infusion with oxygenated blood was followed by pulmonary edema, which excludes the possibility of this mechanism.

The systemic blood pressure rises after occlusion of the common carotid arteries, falls during the infusion (carotid sinus reflex), and then rises again. The maximum level, found toward the end, when the effect of occlusion of the carotid arteries was added to that of increased blood volume, was about 170 mm. of mercury. Therefore no permanent arterial hypertension plays any part in these experiments.

Venous hypertension undoubtedly occurs; extreme figures may be reached for a short time. This may be an important element in the causation of the edema. However, venous infusion under pressure far higher than that obtained by standard carotid infusion, caused pulmonary edema in only a small percentage of the experiments.

Distention of the heart should be considered. The dog's heart dilates tremendously during the infusion, but this distention should not be considered as a manifestation of failure. This is borne out by the slight changes in the electrocardiogram, the preservation of normal rhythm, the moderate auscultatory signs of strain, and by the fact that upon section the heart is often found beating strongly and may even continue to do so after excision. In spite of these facts, distention of the heart may play a part and will be studied later.

The pulmonary edema which is brought about in dogs by the use of interrupted carotid infusion cannot be explained without taking into account factors

which are not purely mechanical. Vascular changes, nervous reflexes, and humoral mechanisms are being investigated and will be reported subsequently.

The evaluation of pulmonary edema produced by our technique must take into account seasonal conditions. We have observed that when experiments were made in the summer, the dogs had poor resistance and died early, often with a more severe pulmonary edema than was produced in other seasons. This can be explained by the fact that dogs have very few sweat glands and depend chiefly upon panting and vaporization of water for keeping their body temperature within reasonable limits.²⁹ This mechanism, which may produce overventilation of the alveoli and may change the chemical composition of the blood³⁰, both stimulates the medullary centers and causes a greater amount of blood to pass through the lungs in a given unit of time. That the latter occurs is demonstrated by the high lung/body index which we found in summer in comparison with that found in early spring. The hyperemia of the lungs, the greater stimulation of the respiratory center, and the frequent alkalosis are all factors that must be taken into consideration.

SUMMARY

1. A new experimental procedure for producing acute pulmonary edema in dogs is described. The basis of the method is the rapid infusion of massive quantities of fluid into the common carotid arteries, toward the head. The infusion is performed in three short, interrupted periods within a half hour, under a pressure of 280 to 300 mm. Hg. The quantity of fluid introduced amounts to 2.3 times the dog's estimated blood volume. This procedure produced pulmonary edema in nearly all experiments.

Clinical manifestations and electrocardiographic, roentgen, and post-mortem findings are discussed.

2. The effect of infusion of either the same amount or a larger amount of fluid into the femoral arteries and into veins has been studied and compared with the results of intracarotid infusion. Pulmonary edema is produced by these methods in only a few experiments.

3. The effect of varying the chemical composition of the fluid is discussed.

4. Neither the amount of fluid injected nor the rate of its injection determines the production of edema. Factors other than mechanical ones are involved in the production of the form of pulmonary edema which is being investigated.

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PAROXYSMAL PULMONARY EDEMA CONSEQUENT TO STIMULATION OF CARDIOVASCULAR RECEPTORS

II. MECHANICAL AND NEUROGENIC ELEMENTS

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A NEW method of producing acute pulmonary edema in dogs based upon rapid intracarotid infusion of massive quantities of fluid toward the head was described in a previous article.¹ Fluid amounting to more than twice the dog's estimated blood volume was infused into the carotid arteries under a pressure of 280 to 300 mm. Hg, in three short interrupted periods, which occupied half an hour in all. The study has been continued in an attempt to evaluate the role of the various mechanical and neurogenic elements in the production of this type of experimental pulmonary edema.

A. MECHANICAL FACTORS

Methods.—The influence of *gravity* was studied by keeping the animal either lying on one side or in the standing position throughout the period of infusion. The influence of dynamic changes secondary to spasm of the glottis was studied by performing a *tracheotomy* either prior to the first infusion or immediately after it. The effects of varying pressure conditions in the respiratory tree were studied by using the following procedures: (a) tracheotomy followed by artificial respiration with an interrupted positive pressure of 8 cm. of water; (b) tracheotomy followed by artificial respiration with an interrupted negative pressure (suction) of 8 cm. of water; and (c) tracheotomy and continuous insufflation of air under a lateral pressure of 10 cm. of water near the carina through a Foley catheter.

The effect of *bleeding* was studied in the following way. Following heparinization, the standard intracarotid infusions were performed. During the second and third infusions, however, amounts of blood equal to the volume of infusion were taken from the femoral artery. The blood obtained during the second infusion was used as the infusion fluid for the third infusion.

Results.—The effect of *gravity* fully explains the congestion which is constantly present in the posterior part of the lungs when the dogs are perfused by means of the standard technique. Dogs kept lying on one side show an intense congestion of the lung on the dependent side which is revealed by the cyanotic color of its surface. However, this congestion does not vary with the edema, as the lung of the upper side is lighter in color, but may be heavier in weight than the other. Dogs kept standing during the experiment show the same intensity of pulmonary edema as the others but exhibit very marked congestion of the lower lobes, both in the back and in the front.

The effect of rapid *bloodletting* during the infusion was demonstrated in a striking way by the fact that the dogs so treated did not show any trace of pul-

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TABLE I. THE EFFECTS OF VARIOUS PROCEDURES WHICH INFLUENCE RESPIRATION

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF DOGS (KG.)	INTERVENTION	INDEX LUNG/ BODY	GRADE OF EDEMA	REMARKS
50	6.4	Tracheotomy	2.74	+++	
89	8		5.4	++++	Summer
97	13		3.46	++++	Summer, premature death
32	10.4	Respiration by suc- tion	3.29	++++	
28	10	Respiration by pressure	1.18	-	
37	6	Respiration by pressure	1.28	-	
41	7	Respiration by pressure	1.07	-	
96	11	Respiration by pressure	1.75	+	Summer. Artificial respiration started after first infusion
73	8.2	Continuous air in- sufflation	1.19	-	
66	8.4	Expiratory valve	1.92	+	Valve in use all of the time
72	12.7	Expiratory valve	1.48	+	Valve applied at the end of first infusion
98	13	Expiratory valve	1.42	+	Valve in use all of the time. Very hot day. Incomplete infusion due to premature death

monary edema, the *lung/body index* ranging from 0.8 to 1.21, as it does in normal dogs.¹

The result of various procedures affecting respiration is shown in Table I.

Tracheotomy does not prevent pulmonary edema. *Artificial respiration by intermittent suction* intensifies the edema. On the contrary, *artificial respiration by either continuous or rhythmic insufflation of air under positive pressure* inhibits the formation of pulmonary edema. The same is true but to a lesser degree, when the resistance against which expiration must take place is increased.

B. NEUROGENIC FACTORS

Methods.—The importance of stimulation of the pressoreceptors of the carotid sinus was investigated (a) by mechanically distending the sinus regions without infusion, and (b) by denervating the carotid sinuses prior to infusion. In addition, some studies were made on the role of the vagus nerve and the sympathetic nervous system.

Mechanical Distention of the Sinus: This experiment was performed in large dogs under morphine (3 mg. per kilogram of body weight) and chloralose (0.1 Gm. per kilogram of body weight) anesthesia by means of a special device composed of a thin ureteral catheter at the end of which a small piece of latex rubber was fixed by means of ligatures. The catheter was connected to a manometer, to a pump with a valve, and to a Marey tambour, and was introduced into the cephalic end of the carotid artery to a point judged to be near the sinus area. The rubber bulb was then distended. If no change in the femoral pressure occurred, the air was allowed to escape through the valve and the sound was pushed 1 to 2 mm. further. After a few attempts a point was found where the distention caused a sudden and marked hypotension, coupled

with bradycardia and respiratory changes. By the use of two ureteral catheters it is possible to stimulate both carotid sinuses at the same time.

Carotid Denervation: If a short interval or none at all was to be allowed before the beginning of the experiment on carotid denervation, morphine-urethane anesthesia was used, as described in the original technique,¹ and asepsis was dispensed with. If an interval of several days was to intervene between the denervation and the experiment, nembutal anesthesia was used and strict asepsis was adhered to. A ligature placed loosely around the common carotid artery provided sufficient traction to bring the bifurcation into view. A delicate mouse-toothed forceps was then used to remove the adventitia and nerve filaments from the entire carotid sinus area. In some experiments painting the sinus area with saturated phenol solution was also carried out. In one dog, infiltration with novocaine was used instead of denervation. Further experiments were made after cutting the vagi and after sympathectomy.

Vagus Section: This procedure was performed in the cervical region. The vagus nerve in dogs contains the depressor nerves and also the sympathetic trunk between the first cervical and stellate ganglion. Owing to the high position of the first cervical ganglion it is very difficult to isolate the real vagal fibers. For this reason the section was made rather low and just before the beginning of the infusion. In one experiment, infiltration of the vagi with 1 per cent procaine was substituted for vagus section.

Sympathectomy: Nembutal anesthesia was used and strict asepsis was adhered to in every case. Intermittent intratracheal insufflation accomplished pulmonary ventilation while the animal's chest was open. A 4-inch muscle-cutting incision along the third intercostal space was made. Gentle traction was made on the stellate ganglion and all rami from it were severed. The posterior parietal pleura was then carefully incised and the second, third, and fourth thoracic sympathetic ganglia were separated from their respective rami communicantes. The chain was removed intact. Hemostasis was secured and the ribs were approximated with heavy silk sutures.

Combined Vagal Stimulation and Intracarotid Infusion: In another type of experiment both intact vagi or the central or the peripheral ends of these nerves, were stimulated by means of a Harvard inductorium. This stimulation was alternated with intravenous infusion of a relatively moderate amount of fluid (from 1.2 to 1.8 times the blood volume) administered in three interrupted periods.

TABLE II. DISTENTION OF CAROTID SINUS BY RUBBER BALLOONS

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOG (KG.)	INTERVENTION	CONGESTION	EDEMA
14A	23	One sinus	+	-
15A	21	One sinus	++	+
16A	28.5	Both sinuses	++	+
17A	34.5	Both sinuses	++	+
18A	36.8	Both sinuses	+	-
26A	18	Both sinuses	+	+
28A	22	One sinus plus slow venous infusion	+	+

Results.—The effects of mechanical distention of the carotid sinus are shown in Table II. A more or less pronounced congestion of the lungs was usually obtained, but no real edema. In some experiments, traces of edema were present in one lobe, but this was not comparable to the edema produced by our newer method¹ of infusion.

Results of denervation of the carotid sinus are shown in Table III. Pulmonary edema was produced in only two dogs out of seven.

TABLE III. RESULT OF STANDARD CAROTID INFUSION IN DOGS WITH PREVIOUSLY DENERVATED CAROTID SINUS

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF THE DOGS (KG.)	INTERVEN- TION	INTERVAL	INDEX LUNG/ BODY	EDEMA	REMARKS
40	16.4	Unilateral	1 hr. 40 min.	2.86	+++	
8	19	Bilateral		1.21	-	Spring
16	27	Bilateral	2 hr. 45 min.	1.09	-	Spring. Incomplete infusion due to pre- mature death
30	23.4	Bilateral	4 days	1.06	-	Spring
33	10.4	Bilateral	Immediate	1.28	-	Spring. Procaine block
114	11	Bilateral	1 hr.	1.21	-	Fall
82	8.2	Bilateral	4 days	1.95	+	Summer
100	20	Bilateral	Immediate	1.95	+	Summer

Cutting the vagus nerves or infiltrating them with procaine had no apparent influence. Dogs so treated apparently died in the same way as the controls, and showed typical pulmonary edema with a high lung/body index. Cutting of the vagus nerves prior to venous infusion did not seem to increase the development of pulmonary edema.

TABLE IV. RESULTS OF SYMPATHECTOMY

SERIAL NUMBER OF EXPERIMENT	WEIGHT OF THE DOGS (KG.)	AMOUNT OF INFUSED FLUID	SIDE OF OPERATION	LUNG/BODY INDEX	EDEMA	SIDE ON WHICH THE LUNG IS HEAVIER
23	12	2.3	Right	2.20	+	Left
35	10.4	3.5	Right	2.69	++	Right
45	13.6	2.6	Right	1.17	-	Right
74	10.7	2.3	Bilateral	3	+++	-

After unilateral sympathectomy there appeared to be a greater resistance to the infusion and a tolerance of greater amounts of fluid (Table IV). On the other hand, unilateral lung changes were indefinite. In some experiments the weight of the lung on the operated side was greater, while in others, the lung on the intact side weighed more. Atelectasis, adhesive pleuritis, or slight unilateral pneumothorax on the operated side may have caused these variations. Moreover, the distribution of sympathetic fibers to the lungs is contralateral as well as ipsilateral.

Stimulation of either the central or the peripheral end of one vagus, the other vagus being intact, did not produce pulmonary edema, even when the venous infusion amounted to 1.8 times the estimated blood volume. Stimulation

of the two intact vagi during venous infusion of 1.8 times the blood volume was followed by severe pulmonary edema. Stimulation of the peripheral end of the cut vagi during a similar infusion caused severe pulmonary edema. Stimulation of the peripheral end of the cut vagi without venous infusion, done as a control, resulted in only slight congestion of the lungs. Stimulation of the central end of the cut vagi during venous infusion caused no pulmonary edema (Table V).

TABLE V. STIMULATION OF THE VAGI

SERIAL NUMBER OF EXPERI- MENT	WEIGHT OF THE DOGS (KG.)	SURGICAL PROCEDURE	AMOUNT OF IN- JECTED FLUID AND RATE OF INJECTION	PRES- SURE OF INJEC- TION (MM. HG)	INTERVENTION	INDEX LUNG/ BODY	EDEMA
15	9	Procaine block of vagi	2.3 Carotid artery toward brain	260		1.8	++
99	10.5	Vagi cut	2.3 Carotid artery toward brain	260		2.9	+++
7	16		1.8 Femoral vein toward heart	100-120	Electric stimulation intact vagi	2.87	+++
110	15		1.8 Jugular vein toward heart	100-120	Electric stimulation intact vagi	2	+++
103	26	Right vagus cut	1.3 Jugular vein toward heart	100-120	Electric stimulation cephalic end left vagus	0.9	-
111	7.5	Vagi cut	1.8 Jugular vein toward heart	100-120	Electric stimulation cephalic end both vagi	1.05	-
106	19	Right vagus cut	1.3 Jugular vein toward heart	100-120	Electric stimulation cardiac end left vagus	1.11	-
112	9.5	Vagi cut	1.8 Jugular vein toward heart	100-120	Electric stimulation cardiac end both vagi	3.65	++++
115	9	Vagi cut			Electric stimulation cardiac end both vagi	0.83	-

DISCUSSION

We had previously demonstrated¹ that the rapid intracarotid infusion of fluid consistently causes pulmonary edema. The part played by the fluid itself when the standard technique was used was recognized as important but not as predominant. It was necessary, therefore, to investigate the part played by the sensitive receptors of the cardiovascular apparatus. Since one of the main results of the infusion is the distention of the carotid sinus, it is apparent that the receptors of this area are very important.

Prolonged mechanical distention of the sinus regions by means of rubber balloons caused severe respiratory and circulatory embarrassment, and occasionally death. As a result, the lungs showed severe congestion, but only occasional and slight edema. This can be attributed to the action of antagonistic mechanisms. On the one hand, a reflex arising in the carotid sinus affects the pulmonary vessels by a mechanism which will be discussed later; on the other

hand, this reflex causes a tremendous drop in systemic pressure and a decreased venous return to the heart, with the result that a relative ischemia of the lungs takes place.

The mechanisms by which a carotid sinus reflex might cause changes in the pulmonary vessels without greatly lowering the venous return are two: (1) distention of the carotid sinus plus artificially increased venous return to the heart (both factors are active in our standard method¹); and (2) distention of the carotid sinus plus the action of a chemical substance maintaining a high pressure in the pulmonary circulation. The latter mechanism will be considered in a subsequent paper.

As for the first mechanism, if our assumption is correct, the two main factors must both be present: neither carotid sinus stimulation alone nor increased venous return alone will cause pulmonary edema. This has been shown to be true. Infusion of fluid alone did not consistently cause pulmonary edema when given by the standard technique: (a) into vessels other than the carotid arteries; (b) into only one carotid artery; (c) into denervated carotid arteries. On the other hand, distention of the carotid sinus did not cause pulmonary edema when: (a) there was no infusion, (b) when increase of venous return was prevented by simultaneous arterial bleeding.

In a few experiments moderate pulmonary edema was produced even when the infusion was made either into veins or into denervated carotid arteries. This occurred mainly during the summer. In the first paper of this series it was pointed out that in summer dogs have a certain degree of dilatation of the pulmonary vessels which is probably connected with the mechanism of panting. However, this dilatation does not completely explain the results mentioned. We believe that these results can be explained only by admitting that, even if carotid sinus reflexes have a paramount importance, other reflexes also play a part in producing the edema. Sensitive receptors are present in the aortic arch,^{2, 11} the venae cavae,³⁻⁵ the right auricle,^{6, 7} the pulmonary veins,^{5, 7, 9} the pulmonary artery,⁸⁻¹³ the auricles,^{5, 6} and the ventricles.^{7, 11, 14, 15} All these receptors are stimulated by the rapid increase in the volume of circulating fluid which takes place in our experiments. However, the aortic receptors are stimulated only moderately, since the systemic blood pressure rises only moderately. The receptors of the venae cavae are highly stimulated, but for only a short time. On the other hand, stimulation of the receptors of the pulmonary artery is likely to cause a reflex dilatation not only of the peripheral vessels but also of the pulmonary vessels.^{9, 10}

The severe and lasting distention of the heart itself also tends to produce a lasting stimulation of the ventricular and auricular receptors. The importance of these receptors has been emphasized in different types of experiments on pulmonary edema,¹⁴⁻¹⁶ and also by the studies of Hochrein¹⁷ which confirmed the existence of a cardiopulmonary reflex which brings about a dilatation of the pulmonary vessels.

Therefore we believe that the following factors should be considered in studying the pathogenesis of pulmonary edema: (a) mechanical distention

of the lung vessels due to fluid injected into the circulation; (b) changes of the lung vessels due to reflexes arising in the carotid sinus; and (c) changes of the lung vessels due to reflexes arising in the other parts of the cardiovascular apparatus, mainly in the heart itself.*

We believe that the role played by seasonal and temperature changes is due only in part to congestion of the lungs which is already present. The other and more important factor is a higher excitability of the nerve centers. This will favor the development of pulmonary edema by causing more intensive reflexes when all the cardiovascular receptors are stimulated and will more readily produce cardiopulmonary reflexes after denervation of the carotid sinus.

Mechanical distention due to fluid alone might undoubtedly be pushed to a point where pulmonary edema would occur with great frequency, whatever the route of injection. However, even were the amount of injected fluid tremendously increased, a large percentage of the dogs would die from acute heart failure without pulmonary edema, as our experiments have shown. It must be concluded, therefore, that the amount of fluid required for intracarotid infusion by our standard method is insufficient of itself to produce pulmonary edema; and that either vasomotor or permeability changes of the lung vessels are necessary factors for the production of the edema.

Our assumption is based partly upon the result of experiments made with denervation of the carotid sinus, partly upon those made by injection into veins, and partly upon pharmacologic experiments, which will be reported in a subsequent paper. Surgical intervention on the carotid sinus is easy. On the other hand, operation on other receptors is impractical.† This is why, after ascertaining the importance of the afferent pathway from carotid sinus to central nervous system, we tried the section of nerve fibers only in the efferent part of the reflex arc.

It is known that the carotid sinus reflex is based upon two different arcs: (a) a carotido-cardiac reflex with the efferent pathway by way of the vagus nerves,¹⁸ which retards the cardiac action; and (b) a carotido-vascular reflex with the efferent pathway through the sympathetic system¹⁹⁻²⁰ which dilates the peripheral vessels.

In spite of the fact that knowledge about the vasomotor innervation of the pulmonary vessels²¹ is still incomplete, it has been shown that a carotido-pulmonary reflex exists, and that its efferent pathway is through the sympathetic system.^{5, 22-24} For this reason we tried to sever the pulmonary connections of the sympathetic ganglia on one side. This resulted in a greater resistance to the development of pulmonary edema, which was demonstrated by the small amount of foam present when greater than standard amounts of fluid were injected.‡ The uncertain result of the comparative study of the operated and intact side is not surprising when one considers the possibility of local causes of

*Extreme bradycardia has to be considered only in those experiments where the distention of the carotid sinus was not accompanied by infusion.

†The denervation of other organs can be accomplished only with open thorax. Artificial respiration necessary in this procedure inhibits the development of edema.

‡Bilateral stellate ganglionectomy was performed on two dogs subsequent to the preparation of this manuscript. The pleural cavity was not entered. Of the two dogs, one had the average pulmonary edema which may have been favored by a severe bradycardia during the infusion periods. The other dog had a minimal foam and an index of 1.3.

error, the multiplicity of nerve fibers, and the fact that sympathetic fibers going to the lungs are partly ipsilateral and partly contralateral.

Stimulation of nerve fibers which are anatomically sympathetic may favor the edema in two different ways: (1) by causing dilatation of the capillaries (it should be remembered that sympathetic vasodilators are cholinergic²⁵); and (2) by directly increasing the permeability of the capillaries, independent of changes produced in the caliber of the vessels. This fact has been demonstrated in the case of the knee joint and was thought to be probably true for the lungs as well.^{26, 27}

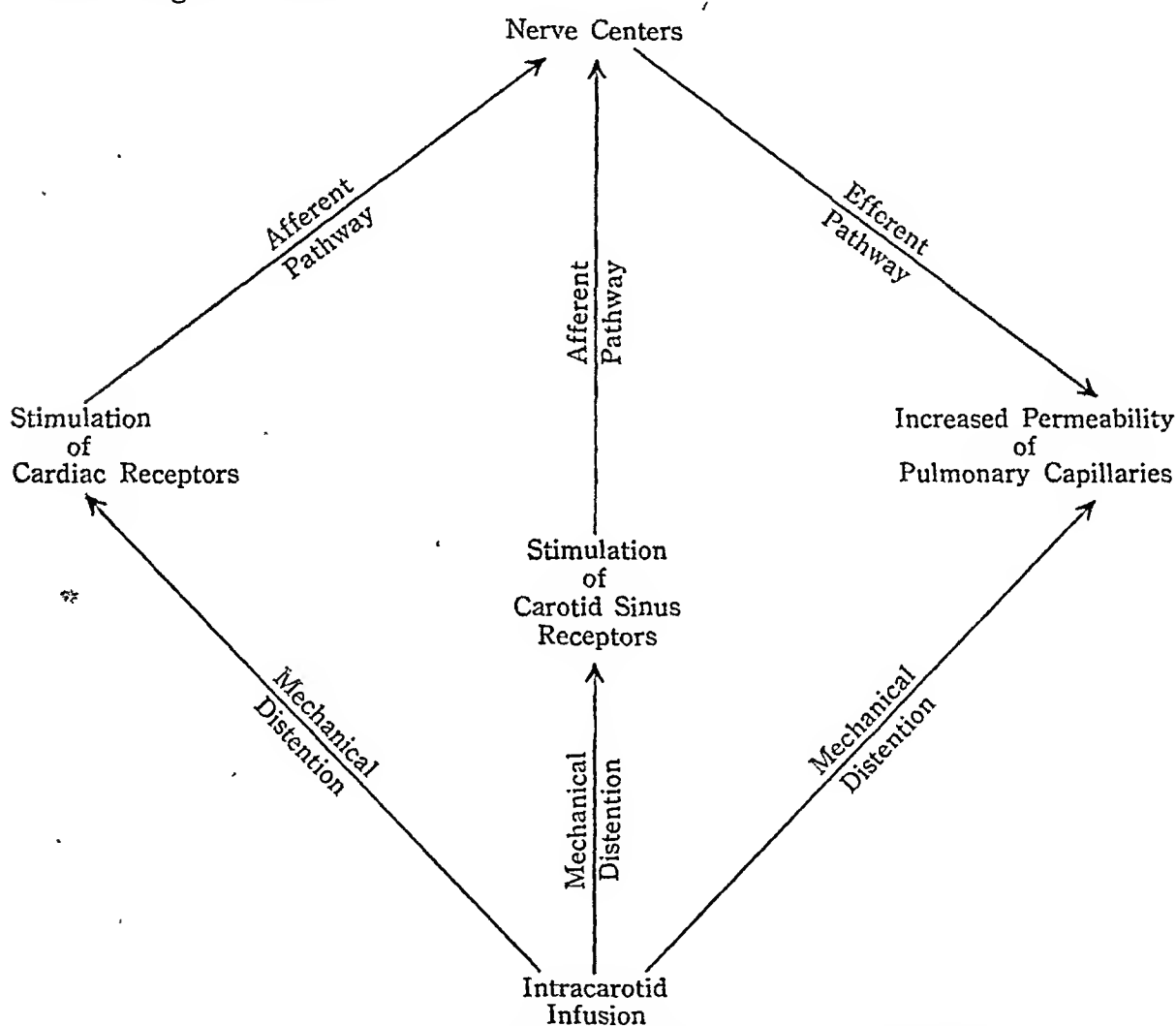


Fig. 1.—Diagrammatic representation of the mechanical and nervous factors which combine to produce the pulmonary edema experimentally induced by intracarotid infusion.

Cutting the vagus nerves, which has been found to increase pulmonary edema produced by venous infusion in cats and rabbits,^{28, 29} did not increase pulmonary edema in our dogs. It likewise did not prevent the production of pulmonary edema by intracarotid infusion.

Stimulation of either the intact vagi or the peripheral end of the cut vagi caused pulmonary edema when the procedure was alternated with venous infusions. We are inclined to attribute this favoring action of the nervous stimulation to the resulting tremendous bradycardia, which at times approached

asystole. It is known that bradycardia favors congestion of the pulmonary vessels.^{28, 31-34}

The importance of glottis spasm and possible bronchospasm in favoring pulmonary edema has been kept in mind. We have frequently seen spasm of the glottis accompanied by two or three deep abortive gasps which caused severe suction on the alveolar wall and on the wall of the lung capillaries. Experiments with rhythmic suction exerted on the trachea have shown that this leads to early and intense edema. However, even if spasm of the glottis favors the edema, it is not the main factor involved since tracheotomy does not diminish the edema. It is difficult to evaluate bronchospasm which is detected by auscultation, as a cause of a similar suction during inspiration.

The importance of the pressure existing in the bronchi and alveoli was first demonstrated in adrenalin-produced pulmonary edema,³⁵⁻³⁸ then in pulmonary edema produced by ligature of the aorta,³⁹ and later in pulmonary edema caused by poison gas.⁴⁰ Our experiments have shown that either a rhythmic or a continuous increase of intratracheal pressure leads to inhibition of the edema. As our type of experimental edema is comparable to the extremely sudden and lethal type of human pulmonary edema, our experiments confirm the opinion that positive pressure may be useful in this syndrome.^{38, 40} The action of the expiratory valve is probably more of a factor in experimental animals, which are strong and vigorous, than in patients, whose expiratory muscles may be unable to overcome the obstacle.

SUMMARY

The part played by mechanical and neurogenic factors in pulmonary edema experimentally produced in dogs by the use of a standard technique has been investigated. The basis of this standard technique is the rapid, interrupted infusion of saline solution into the carotid arteries toward the brain.

1. The quantity of injected fluid may be considered as submaximal, in the sense that, while the fluid favors the development of edema by distending the pulmonary vessels, the amount of fluid administered is insufficient of itself to produce edema.

2. The importance of specific receptors of the cardiovascular apparatus has been demonstrated. Their stimulation causes a reflex leading to increased permeability of the pulmonary capillaries, and favors the development of edema if these vessels are already distended. The problem of whether the reflex causes first a dilatation of the vessels, or whether its effect is the result of a direct increase of permeability needs further study. The most important among these reflexes is the carotido-pulmonary reflex whose afferent pathway to the central nervous system is through the glossopharyngeal nerve, and whose efferent pathway to the lungs is through fibers which are anatomically part of the sympathetic system. Another important reflex is that elicited by distention of the heart chambers. A third reflex, whose importance cannot yet be measured, is the pulmonary artery-pulmonary vessels reflex. All these reflexes are able to cause pulmonary edema when a submaximal quantity of fluid, in itself insufficient to produce edema, is injected into the circulation.

3. Deeper understanding of the mechanism can be obtained only by using drugs either to enhance or to inhibit the edema, and by studying by means of biologic assay the properties of both the blood and the edema fluid.

4. Electrical stimulation of either the cardiac end of the cut vagi or the intact nerves favors pulmonary edema by causing extreme bradycardia. This factor, however, does not play any role in the experiments of infusion with standard technique.

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PAROXYSMAL PULMONARY EDEMA CONSEQUENT TO STIMULATION OF CARDIOVASCULAR RECEPTORS

III. PHARMACOLOGIC EXPERIMENTS

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A NEW method for inducing acute pulmonary edema in dogs has been described in previous publications.^{1, 2} The method is based upon the rapid intracarotid infusion of physiologic salt solution cephalad. A quantity of fluid equivalent to more than twice the estimated blood volume of a dog is injected within twenty minutes, in three separate portions, at a pressure of 280 to 300 mm. of mercury. This method almost always results in the production of very severe pulmonary edema (nine out of ten dogs in the control series showed severe pulmonary edema). Different types of fluid, including Ringer's, Tyrode's, bovine albumin solution, and dog blood were successively studied. It has also been shown that infusion into other vessels by the same technique does not cause pulmonary edema with the same consistency as does infusion into the carotid arteries.²

In a former communication³ the relation of different mechanical and neurogenic factors to pulmonary edema were studied. The beneficial action of artificial respiration under positive pressure was demonstrated. The most striking procedure for the prevention of edema of the lungs was denervation of the carotid sinuses prior to the infusions. Cutting of the vagus nerves did not change the outcome. The conclusion reached was that acute pulmonary edema caused by the rapid intracarotid infusion of physiologic solutions is a syndrome which is only indirectly caused by the flooding of the circulatory system. The quantity of fluid introduced is submaximal and does not per se produce pulmonary edema. The increased fluid volume does place a heavy strain on the organs of the circulatory system and initiates multiple reflexes. Among these, a carotid sinus-pulmonary reflex is of paramount importance. A cardiopulmonary reflex is also significant. The afferent stimuli follow different routes; the efferent stimuli reach the lungs along sympathetic fibers.

It was thought that pharmacologic experiments might yield additional information as to the mechanism of this type of experimental pulmonary edema and also suggest the best treatment of this paroxysmal syndrome. These experiments are the subject of this paper.

Previous investigation of the treatment and prevention of acute pulmonary edema has been chiefly through clinical studies. A review of these studies was

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published in 1942 by one of the authors (A. A. L.).⁴ In 1928, one of the authors (A. A. L.) systematically studied treatment of pulmonary edema induced in rabbits by the intravenous injection of a massive dose of adrenalin.⁵ There followed a study by Antoniazzi⁶ on the pulmonary edema of rabbits caused by ligation of the aortic arch. Sporadic experiments were made by Brunn,⁷ using luminal, and by Farber,⁸ using atropine.

TABLE I

DRUG	SOLUTION (%)	DOSES (MG./KG.)	REMARKS
Morphine sulfate	1-6.5	3-32	-
Sodium phenobarbital	2	25-100	-
Sodium barbital	5	100-350	-
Chloral hydrate	5	150-290	-
Atropine sulfate	0.01-0.1	0.04-0.8	-
Scopolamine hydrobromide	0.1	0.3-0.5	-
Demerol, Winthrop	1	25-40	-
Syntropan, Roche	0.5	1.5-2	-
Trasentine hydrochloride, Ciba	5	2.5-3	-
Papaverine hydrochloride, Lilly	15-50	5-30	-
Curare (Intocostin, Squibb)	0.5-1	1.35-1.8	-
Sodium nitrate	5	60	-
Acetyl- β -methylcholine (Meecholy, Merck)	1	0.14-1.5	-
Physostigmine hydrochloride	0.1	1-4	High doses only in association with atropine
Prostigmine, Roche	0.1	0.05-1	High doses only in association with atropine
Procaine, Abbott	5	20-100	-
Nupercaine, Ciba	0.06	1.6	-
Ergotamine tartrate (Gynergon, Sandoz)	0.1	0.2-0.4	-
2-diethylamino-ethyl-1,4-benzodioxan (883 F—Soc. Parisienne Expans. Chim.)	-	4.5-9	-
Quinine dihydrochloride	5	25-70	-
Mercupurin, Campbell	10	10	In association with aminophylline
Aminophylline, Searle	5	54	-
Pitressin, Parke-Davis	-	2.7 units	-
Adrenalin hydrochloride (Supra-renaline, Armour)	0.01-0.00001	0.3-0.5	-
Metrazol, Billhuber-Knoll	10	20	-
Coramine, Ciba	25	30	-
Cedilanid, Sandoz	-	0.5 (cat units)	-
Digilusin, Lilly	-	0.5 (cat units)	-
Strophosid, Sandoz	-	0.33-0.36 (cat units)	-

TECHNIQUE

The present study was made on 98 mongrel dogs. The technique of infusion into the carotid arteries is that described previously.¹ The fluid used in these experiments was 0.85 per cent sodium chloride solution. The injection of drugs was nearly always made into an exposed jugular vein. Exceptions will be reported in the sections dealing with the results. In nearly all experiments the anesthesia was that previously described¹ and called "standard"; namely, morphine sulfate (3 mg. per kilogram of body weight), injected subcutaneously,

and urethane (1 to 1.3 Gm. per kilogram of body weight), given by stomach tube thirty to sixty minutes later. The relatively small number of experiments performed with each drug allowed definite conclusions because of the fact that physiologic salt solution, infused by the technique described, almost without exception produced severe pulmonary edema in control animals.²

RESULTS AND COMMENTS

Hypnotics.—Animals given large doses of morphine prior to the infusion differed markedly from the controls, which in accordance with the standard technique were given only three mg. of morphine sulfate per kilogram of body weight. After large doses of morphine the dogs subjected to infusion gave evidence of only mild dyspnea and showed no agitation and no spasm of the glottis. The *lung/body index** was only slightly increased, and only a trace of foam was found in the dependent lobes of the lungs (Table II). Therefore, morphine is of definite value in preventing pulmonary edema induced by this standard technique, even if not completely successful.

TABLE II. HYPNOTICS

NO.	DRUG USED FOR ANESTHESIA	HYPNOTIC IN MG./KG. AND ROUTE	LUNG/BODY* INDEX	GRADE† OF EDEMA
12		Morphine, 30 subcutaneous and intravenous	1.40	+
120	Urethane, standard‡	Morphine, 30 subcutaneous and intravenous	1.34	+
13	Morphine, standard‡	Phenobarbital, 59 intravenous	1.63	+
121	Morphine, standard	Phenobarbital, 100 intravenous	1.06 (Incomplete infusion)	-
125	Morphine, standard	Phenobarbital, 70 intravenous	1.05	-
6	Morphine, 10 mg./kg.	Phenobarbital, 25 intravenous	1.25	-
152	Morphine, 15 mg./kg.	Phenobarbital, 40 intravenous	1.08	+
24	Morphine, standard	Barbital, 220 intravenous	1.35	-
29	Morphine, standard	Barbital, 100 intravenous	2.68	+++
122	Morphine, standard	Barbital, 350 intravenous	1.25	-
153	Morphine, 16 mg./kg.	Barbital, 125 intravenous	1.20	-
123	Morphine, standard	Chloral hydrate, 230 intravenous	1.38	-
124	Morphine, standard	Chloral hydrate, 230 intravenous	1.11	-
154	Morphine, standard	Chloral hydrate, 290 intravenous	0.96	-
151	Morphine, 13 mg./kg.	Chloral hydrate, 150 intravenous	1.75	++
187	Morphine, 8.5 mg./kg.	Chloral hydrate, 260 intravenous	1.20	+

*The lung/body index is the ratio of lung weight in grams to body weight in kilograms.

†The severity of the edema is graded from + to ++++ on the basis of the lung/body index and of the amount of foam.²

‡Standard doses used for anesthesia have been given under "technique."

Next, two barbiturates, phenobarbital and barbital, were studied. The sodium salt of each was given intravenously. Owing to the narcotic action of these drugs, we dispensed with the use of urethane. Both drugs completely prevented edema in four of six dogs. The fifth dog showed only a trace of edema, and the sixth, which exhibited more edema, had received a much smaller dose of barbital. None of the dogs had severe dyspnea, and in some experiments the *lung/body index* was normal. The combination of morphine with barbiturates, which was tried in three additional experiments, with similar positive

*The lung/body index is the ratio of lung weight in grams to body weight in kilograms.

results, allowed a marked decrease in the dose of barbiturates. It was found that the optimal dose of the single drugs per kilogram of body weight was about 70 to 100 mg. of sodium phenobarbital and 220 to 300 mg. of sodium barbital.

Doses of 230 to 300 mg. of chloral hydrate per kilogram of body weight completely prevented pulmonary edema in four of five dogs. Combination of this drug with morphine was also successful if the dose of chloral hydrate was not decreased too much. Chloral hydrate was interesting because it was effective in amounts which are comparable to those used clinically.

We used hypnotics in experiments on sixteen dogs. In spite of the varying doses which we used in seeking the optimum, severe pulmonary edema developed in only one dog, mild pulmonary edema developed in a second, and minimal edema developed in five more. That nine of the sixteen animals had no trace of edema is striking when compared with the very high percentage of animals in the control series² (approximately nine-tenths) which showed severe pulmonary edema.

Local Anesthetics.—Procaine was injected in doses of 30 to 60 mg. per kilogram of body weight either subcutaneously or by intracarotid or intrajugular injection. When the subcutaneous route was used, part of the dose was injected before and part between the infusions. The results of early experiments seemed satisfactory, but in later experiments the outcome was inconstant. Five out of 13 dogs died of severe pulmonary edema, three had high lung/body indices, with almost no foam, and three had no edema (Table III). It was concluded that some of the properties of procaine were useful, but that others promoted the edema. Depression of the excitability of the pressoreceptors should help in preventing this type of experimental pulmonary edema. Two actions of local anesthetics which most often promote the edema are: (a) sensitization of the vessels to the action of adrenalin and (b) stimulation of the cortex of the brain.

TABLE III. LOCAL ANESTHETICS

SERIAL NUMBER OF EXPERI- MENT	DRUG	ROUTE OF ADMINISTRA- TION	DOSE (MG./KG.)	ASSOCIATE DRUG AND DOSE (MG./KG.)	INDEX LUNG/BODY	GRADE OF EDEMA
62	Procaine	Subcutaneously	30	-	1.68	+
63	Procaine	Subcutaneously	60	-	1.29	-
69	Procaine	Subcutaneously	60	-	2.9	+++
70	Procaine	Subcutaneously	40	-	4.35	++++
71	Procaine	Subcutaneously	32	-	1.34	-
75	Procaine	Subcutaneously	30	-	1.89	+
76	Procaine	Subcutaneously	60	Ergotamine tar- trate, 0.3	2.52	+++
131	Procaine	Intracarotid	100	-	1.41	+
132	Procaine	Intracarotid	60	Morphine sulfate, 10		Early death
133	Procaine	Intravenous	60	-	1	-
134	Procaine	Intravenous	60	-	2.4	++++
135	Procaine	Intravenous	20	Sodium barbital, 70		Early death
162	Procaine	Lumbar	2.5	-	3.66	++++
171	Nupercaine	Subcutaneously	1.6	-	4.1	++++

The addition of either ergotamine, barbital, or morphine to the procaine did not seem to affect the results. The fact that all early deaths were accompanied by convulsions confirmed the impression that cortical stimulation was present and that the tolerance of the brain centers to the abnormal conditions imposed by the high pressure infusions was decreased. The convulsions were more severe when the injection of the drug was intravascular than when it was subcutaneous. In one experiment with spinal anesthesia, the edema was severe. Nupercaine, tried in another experiment, did not prevent severe edema from occurring.

Autonomic Blocking Drugs.—Atropine was first investigated. Five experiments were performed, with doses varying between 0.04 mg. and 0.8 mg. per kilogram of body weight. The outcome was consistently poor. The animals had more severe pulmonary edema than usual, so that the lungs weighed from three to five times more than normal. The combination of atropine and morphine was used in two experiments. This combination prevented pulmonary edema in one dog, but was not effective in the second animal (Table IV). Although the substitution of scopolamine for atropine, in doses varying between 0.3 mg. and 0.75 mg. per kilogram body weight produced somewhat better results, they were not comparable to those attained with other more beneficial drugs (Table IV).

A comparison of the effects of the various drugs leads one to attribute the poor results in the atropinized dogs mainly to drug stimulation of the nerve centers, which favored the functioning of reflexes. It might also be mentioned that after the administration of atropine, sympathetic reflexes became more active. In the light of the experimental results mentioned, the beneficial in-

TABLE IV. AUTONOMIC BLOCKING DRUGS

SERIAL NUMBER OF EXPERI- MENT	DRUG	DOSE (MG./KG.)	ASSOCIATE DRUG AND DOSE (MG./KG.)	INDEX LUNG/BODY	GRADE OF EDEMA
9	Atropine	0.8	Morphine, standard	4.63	++++
21	Atropine	0.3	Morphine, standard	4.92	++++
87	Atropine	0.04	Morphine, standard	1.98	++
116	Atropine	0.05	Morphine, 15	1.26	-
117	Atropine	0.05	Morphine, 15	3.33	++++
144	Scopolamine	0.5	Morphine, standard	1.53	+
146	Scopolamine	0.75	Morphine, standard	2.75	+++
147	Scopolamine	0.3	Morphine, standard	1.90	+++
42	Ergotamine	0.2	Morphine, standard	1.92	+
47	Ergotamine	0.4	Morphine, standard	1.93	+
48	Ergotamine	0.3	Morphine, standard, and atropine, 0.25	1.80	++
20	883 F	9.0	Morphine, standard	1.24	Incomplete infusion
36	883 F	8.0	Morphine, standard	1.0	+
49	883 F	4.5	Morphine, standard, and atropine, 0.35	3.27	++++
14	Curare (Intocostrin)	1.8	Morphine, standard	1.4	Artificial respiration
79	Curare (Intocostrin)	1.6	Morphine, standard	1.7	+
126	Curare (Intocostrin)	1.35	Morphine, standard, and nembutal, 4.5	1.29	+

fluence of atropine in human pulmonary edema⁴ should certainly be questioned. As far as the mechanism of the attack is concerned, the above experiments show that vagus stimulation is not one of the direct causes of the edema and may even counteract those stimuli which more directly favor the increased permeability of the lung vessels. Among the vagal reflexes which may normally protect the lung vessels, the pulmonary hemodynamic reflex¹⁵⁻¹⁷ is probably the most important.

Two sympatholytic drugs were tried, ergotamine tartrate and 883 Fourné (2-diethylamino-ethyl-1,4-benzodioxan).²² Both acted favorably in the type of pulmonary edema which we are studying. It is interesting to note that dogs treated with ergotamine developed very little foam, though their *lung/body index* was rather high in comparison to that of normal dogs. On the contrary, 883 Fourné seemed to prevent both the formation of foam and the high index (Table IV).

Both drugs may cause premature death of the animals during the infusion because of the extreme bradycardia which may progress to cardiac standstill. Knowing that severe bradycardia per se favors lung congestion,² one may ask whether this fact alone can explain the high index. The addition of atropine did not improve the results, and in one experiment produced poorer results. However, since the poor results of atropine are probably due to central stimulation, this fact is not surprising.

Curare gave excellent results when used in large amounts. However, the use of this drug required positive pressure artificial respiration, which alone is sufficient to prevent this type of pulmonary edema. A smaller dose of curare produced fair results. An even smaller dose in combination with a small dose of nembutal* produced good results. We have concluded that curare helps to

TABLE V. ANTISPASMODIC AND DEPRESSANT DRUGS

SERIAL NUMBER OF EXPERI- MENT	DRUG	DOSE (MG./KG.)	ANESTHESIA	INDEX LUNG/BODY	GRADE OF EDEMA	REMARKS
172	Papaverine	15	Standard	2.1	++	-
176	Papaverine	30	Standard	2.7	+++	-
158	Papaverine	5	Standard	1.16	-	-
137	Demerol	40 subcutaneous	Urethane	-	-	Premature death
			standard			
138	Demerol	30 subcutaneous	Urethane,	0.9	++	Abdominal hem-
			standard			orrhage
139	Demerol	25 intravenous	Standard	1.74	++	-
136	Syntropan	2 intravenous	Standard	-	-	Premature death
140	Syntropan	1.5 intravenous	Standard	1.17	-	-
141	Syntropan	1.5 intravenous	Standard	1.96	++	-
179	Trasentine	3 intravenous	Standard	1.04	+	-
182	Trasentine	3 intravenous	Standard	1.11	+	-
186	Trasentine	2.5 intravenous	Morphine	2.12	+++	-
			mg. 10/kg.			
39	Quinine	70	Standard	2.7	+++	-
143	Quinine	25	Standard	2.51	+++	-

*Nembutal and curare have a synergistic action as far as the central nervous system is concerned.²³

prevent pulmonary edema, probably because the central and gangliar depression produced by this drug limits the intensity of the reflexes. Further studies with eurare will be reported upon later.

Antispasmodic and Depressant Drugs.—Papaverine did not seem to exert any beneficial action in preventing pulmonary edema in our experiments. However, since a combination of papaverine and morphine gave good results, it is possible that papaverine may enhance the favorable action of morphine.

Demerol did not seem as valuable as morphine. A large dose of demerol caused premature death from tonicoclonic contractions of the muscles as soon as the infusion was started; smaller doses, on the other hand, did not prevent the pulmonary edema. We had the impression that demerol stimulated the brain centers, and mainly the respiratory center, an action which favors the onset of pulmonary edema. Syntropan gave better results than demerol, but tonicoclonic contractions, which give evidence of cortical hyperexcitability, were again observed.

Trasentine seemed the best of the series. We had favorable results in two of three experiments. Quinine, on the contrary, did not confer any protective effect.

TABLE VI. AUTONOMIC STIMULATING DRUGS

SERIAL NUMBER OF EXPERI- MENT	DRUG	DOSE (MG./ KG.)	ROUTE OF FLUID INFUSION	AMOUNT OF FLUID AS COM- PARED WITH ES- TIMATED BLOOD VOLUME*	INDEX LUNG/BODY	GRADE OF EDEMA
18	Mecholyl	1	Femoral veins	2	1.66	+++
184	Mecholyl	0.14	Carotid arteries	2.3	3.77	++++
22	Physostigmine	1.2	Carotid arteries	1	2.62	++++
156	Adrenalin	0.5	One carotid artery	2.1	4	++++
161	Adrenalin	0.5	One jugular vein	2.3	1.61	++
163	Adrenalin	0.4	Jugular veins	2.3	1.89	+++
170	Adrenalin	0.3	Carotid arteries	2.3	4	++++

*The blood volume was estimated as equal to 10 per cent of the body weight.

Autonomic Stimulating Drugs.—In our experiments, drugs stimulating the parasympathetic system either directly, like mecholyl, or indirectly, like physostigmine, caused early death during the infusion, by producing cardiac standstill. This was not surprising, since intracarotid infusion under high pressure stimulates the pressoreceptors of the carotid sinus. If no drug is given, slowing of the heart rate because of the carotid sinus reflex is soon compensated for by the antagonistic Bainbridge reflex, which distention of the large veins initiates by the infused fluid. When, on the contrary, either an acetylcholine-like substance (mecholyl) or a substance which inhibits the cholinesterase (physostigmine) is acting, the effects of stimulation of the vagus nerve are increased and the intracarotid infusion is followed by a severe bradyardia and even by early death from pulmonary edema. The use of either drug leads to pulmonary edema even when venous infusion is used. This is easily explained, because stimulation of the peripheral end of the vagus nerve during venous infusion also consistently leads to pulmonary edema. This fact has already been discussed,⁴ and it was observed that the favoring element is brady-

cardia, a hemodynamic factor which leads to dilatation of the pulmonary vessels. Consideration of direct action of acetylcholine in promoting edema of the lungs cannot be excluded, for, when injected intradermally, acetylcholine forms a wheal. However, experiments using physostigmine in combination with atropine disprove this hypothesis.

Adrenalin promotes the production of pulmonary edema by our standard method. This was proved by the fact that either addition of the drug to the fluid or its intravenous injection in graded doses led to an enormous formation of foam and to very high lung/body indices. Moreover, addition of adrenalin to the fluid led to pulmonary edema when infusion was made into the jugular veins. Adrenalin promotes increased venous return in dogs through dilatation of the hepatic veins.²⁸ This increased venous return, together with the stimulation of the myocardium and the increased peripheral resistance also caused by adrenalin, raises the pressure in the pulmonary vessels and dilates them. Stimulation of both the aortic and the carotid pressoreceptors in the intervals between infusions will increase the intensity and the duration of those reflexes which favor the development of pulmonary edema. On the other hand, if the distention of the ventricles favors the production of edema through reflexes, adrenalin may slightly counteract this part of the mechanism by stimulating the myocardium. It is further to be noted that if stimulation of the sympathetic nerves increases the capillary permeability, as recent studies indicate,²⁹ injection of adrenalin should produce the same result.

Hyper- and Hypotensive Drugs, Diuretics.—Experiments with sodium nitrate, a drug exerting a hypotensive and vasodilating action, resulted in a mildly beneficial action. The lung/body index was rather high in two out of three experiments, but the foam was scanty in all three (Table VII). This result may be attributed to a decrease of the venous return due to extreme dilatation of the peripheral arteries. The same action in moderating the severity of the edema was not developed by aminophylline, a vasodilator and diuretic drug, even when Mereupurin, a mercurial diuretic, was added (Table VII). The difference be-

TABLE VII. HYPER- AND HYPOTENSIVE DRUGS: DIURETICS

SERIAL NUMBER OF EXPERI- MENT	DRUG	DOSE (MG./KG.)	WAY OF FLUID INFUSION	AMOUNT OF FLUID AS COM- PARED WITH ES- TIMATED BLOOD VOLUME	INDEX LUNG/BODY	GRADE OF EDEMA
157	Sodium nitrate	60	Carotid arteries	2.3	1.67	+
160	Sodium nitrate	40	Carotid arteries	2.3	1.65	+
180	Sodium nitrate	40	Carotid arteries	2.3	1.21	+
168	Metrazol	20	Carotid arteries	2.3	1.6	++
169	Metrazol	20	Carotid arteries	1.6	2	+++
				Early death		
174	Coramine	30	Carotid arteries	2.3	2.3	+++
173	Aminophylline	54	Carotid arteries	2.3	1.88	++
178	Aminophylline plus mercu- purin	50	Carotid arteries	2.3	2.1	+++
181	Pitressin	2.7 Units	Carotid arteries	1.65	4	++++

TABLE VIII. DRUGS STIMULATING THE MYOCARDIUM

SERIAL NUMBER OF EXPERIMENT	DRUG	DOSE (CAT UNITS PER KG.)	INDEX LUNG/BODY	GRADE OF EDEMA
142	Strophosid	0.36	1.24	++
175	Strophosid	0.33	1.6	+
177	Strophosid	0.33	3.79	++++
145	Cedilanid	0.5	3.75	++++
159	Digiglusin	0.5	2.22	+++

tween the action of sodium nitrate and that of aminophylline may be explained by the facts that aminophylline is a stimulant of the central nervous system and exerts special action on the medulla, and that it stimulates also the chemoreceptors of the carotid and aortic bodies.

Metrazol and coramine did not seem to affect the outcome of the experiment, except for the fact that doses which were too large caused early death during the infusion (Table VII). Both drugs stimulate the nerve centers and especially the respiratory center.

Pitressin was tried in one experiment, which resulted in early death and enormous pulmonary edema. Even though pitressin may decrease both the caliber and the permeability³¹ of the lung capillaries, its effect is not sufficient to prevent pulmonary edema. It is apparent that the peripheral constriction of the capillaries of the greater circulation and the decreased filtration of fluids into the tissues of the body and into the serous cavities caused by pitressin more than offset any favorable action of this drug. The depressive action of pitressin on the diuresis may also be expected to act unfavorably.

Drugs Stimulating the Myocardium.—We performed three experiments with a strophanthin preparation, strophosid, and two with two different digitalis preparations, cedilanid and digiglusin. The drugs were injected intravenously before cannulation of the arteries, i.e., about thirty minutes before the beginning of the first infusion. Digitalis preparations did not affect the outcome. Strophanthin seemed to exert a slightly beneficial action in preventing pulmonary edema. One of three dogs had a low lung/body index and one had relatively scanty foam. This result may be attributed to the fact that digitalis and digitalis-like glycosides stimulate the myocardium and decrease the distention of the ventricles when these are submitted to a severe strain. We have observed that ventricular distention may be considered as a secondary cause of the type of pulmonary edema we are studying, because it stimulates the ventricular receptors. Therefore, it seems logical that strophanthin would have a slightly beneficial action in preventing pulmonary edema. Should pulmonary edema be caused by failure of the left ventricle, a much more striking result would take place. The difference in action between the glycosides of strophanthus and those of digitalis is due to the fact that the former acts much more quickly.

Physostigmine or Prostigmine in Association With Protective Drugs.—As described in a previous paragraph, physostigmine promotes the development of the type of experimental pulmonary edema which we are studying. However, if atropine is added to physostigmine, the result is reversed (Table IX).

Of three dogs, two developed no pulmonary edema, and one (in the summer) had only a slight trace of foam.* The most probable explanation of these results is the following: (a) Physostigmine, used alone, produces pulmonary edema by causing extreme bradycardia and asystole. (b) If the bradycardia is prevented by atropine, the physostigmine is free to exert its central depressant action,^{35, 36} which helps to prevent reflexes which favor pulmonary edema. The addition of another central depressant, morphine, gave very satisfactory results.

TABLE IX. PHYSOSTIGMINE OR PROSTIGMINE PLUS ALLIED DRUGS

SERIAL NUMBER OF EXPERI- MENT	PHYSOSTIGMINE OR PROSTIGMINE (DOSE IN MG./KG.)	ATROPINE OR SCOPOLAMINE (DOSE IN MG./KG.)	CURARE OR MORPHINE (DOSE IN MG./KG.)	INDEX LUNG/ BODY	GRADE OF EDEMA	REMARKS
19	Physostigmine 2	Atropine 0.2	-	1.15	-	-
26	Physostigmine 1.4	Atropine 0.17	-	1.09	-	-
107	Physostigmine 2	Atropine 0.5	-	1.75	+	Summer
118	Physostigmine 1	Atropine 0.1	Morphine 16	1.13	-	-
127	Physostigmine 3	Atropine 0.2	Curare 4	1.33	-	-
101	Prostigmine 0.5	Atropine 0.1	-	1.8	+	Summer
106	Prostigmine 0.05	Atropine 0.05	-	2.1	+	Summer
108	Prostigmine 0.25	Atropine 0.2	-	3.1	+++	Summer
129	Prostigmine 0.5	Atropine 0.3	-	1.12	+	Summer
148	Prostigmine 0.4	Scopolamine 0.3	-	2.54	+++	-
185	Prostigmine 0.8	Atropine 0.1	-	5	+++	-
119	Prostigmine 0.3	Atropine 0.1	Morphine 16	1.11	-	-
128	Prostigmine 0.9	Atropine 0.3	Curare 3	1.5	-	-
130	Prostigmine 0.8	Atropine 0.2	Curare 3	1.3	-	-
149	Prostigmine 1	Scopolamine 0.4	Curare 4.6	1.3	+	-
150	Prostigmine 0.8	Atropine 0.1	Curare 6	1.17	-	-

The considerations mentioned and the observation that large doses of physostigmine cause muscular twitchings and cramps which may even impair respiration led us to combine curare with physostigmine. As far as the peripheral nerves are concerned, the action of curare is antagonistic to that of physostigmine. Therefore, a combination of the two drugs should have no peripheral action whatsoever. However, curare has a depressant action on the ganglia and on the central nervous system^{24, 25} which strengthens the central depression caused by prostigmine.²⁵ Very satisfactory results were obtained in experiments in which physostigmine, atropine, and curare were combined (Table IX). It should be observed, therefore, that the central and not the peripheral action of physostigmine is the more important factor in the prevention of pulmonary edema. As atropine, used alone, favors pulmonary edema, it is advisable to give only the amount of this drug necessary, and no more. Theoretically, atropine might be dispensed with whenever curare is added to physostigmine. However, curare prevents vagus action only in very large doses and this effect is transitory.³⁸ Therefore, in spite of the desirability of simplifying the experiments, a small dose of atropine is necessary.

Prostigmine should exert a central depressant action in smaller doses than physostigmine. For this reason it was tried, in combination with atropine, in doses from one-fourth to one-fortieth as large as those of physostigmine.

*The importance of environmental temperature has been discussed in previous papers.^{2, 2}

These doses proved to be too small. However, when either morphine or curare was added, the results of the use of prostigmine were excellent (Table IX). We must conclude that prostigmine is not so effective in the prevention of pulmonary edema as physostigmine, but that it is just as effective when combined with other drugs having a depressant effect on the central nervous system (morphine, curare). In its favor are its efficacy in smaller doses and the more prolonged duration of its effect.

The excellent results obtained by the combination of a mixture of curare (or morphine) and physostigmine (or prostigmine) with a small protective dose of atropine are shown by the fact that, of seven dogs so treated before and during infusion, only one had even a minimal trace of pulmonary edema. The substitution of scopolamine for atropine does not offer any advantages.

Intravenous injection of curare-atropine-prostigmine in a normal unanesthetized dog was well tolerated. The only visible effects were immediate diarrhea and weakness of the limbs for a few minutes.

GENERAL CONSIDERATIONS ON THE MECHANISM OF PULMONARY EDEMA

As we have already stated in a previous publication,³ pulmonary edema produced by our technique is the expression of a diffuse attempt quickly to get rid of the tremendous amount of fluid which is injected. However, this pulmonary manifestation is so important that it may bring about the death of the animal. That it has special features and a special mechanism are shown by the fact that the pulmonary edema may be prevented by various devices (bleeding, artificial respiration, denervation of the carotid sinus), at times without interfering with other features of the general syndrome. Pharmacologic studies throw further light on the mechanism of pulmonary edema. It is entirely possible to prevent the occurrence of this type of pulmonary edema by use of hypnotics. This confirms the hypothesis that a reflex mechanism, having its starting point mainly in the carotid sinus, and possibly also within the heart itself, favors the occurrence of the edema. The exact localization by the use of different hypnotics of the nerve centers involved did not prove successful. However, the fact that morphine had a useful action suggests involvement of the respiratory center, or at the least shows that the prevention of dyspnea is important, by excluding a mechanical factor favoring the edema. The beneficial action of chloral hydrate in preventing pulmonary edema cannot be explained by the fact that it produces secondary dilatation of the peripheral vessels. The action of the barbiturates points more to involvement of the brain stem in the mechanism of pulmonary edema. Further studies are suggested by the facts that stimuli initiated in the carotid sinus reach the brain along the glossopharyngeal nerve and that the center of the water metabolism, located in the middle brain, is probably playing an important role whenever the blood volume is more than tripled within a short time.

Parasympatholytic drugs had a harmful effect. The effect of atropine was more harmful than that of scopolamine. This indicates that a carotido-vagal reflex is not involved in pulmonary edema, and that moderate vagal stimulation

might even help in preventing the edema. On the other hand, extreme bradycardia is not a favorable factor in preventing the edema, because it tends to cause hyperemia of the lungs. The stimulation of the central nervous system caused by atropine and the slight depression caused by scopolamine may account for the slightly different results obtained by the use of these two drugs. The useful action of sympatholytic drugs such as ergotamine and 883 Fournneau suggests that a carotido-sympathetic reflex (and possibly a less important cardio-sympathetic reflex) are involved in the mechanism of the edema. This would not be surprising, for a carotido-sympathetic reflex has been found to be the cause of the fall in blood pressure which follows distention of the carotid sinus.²¹ The inconstant results obtained with sympatholytic drugs may be explained by the fact that whenever unbalanced vagus action is allowed to take place, distention of the carotid sinus causes extreme bradycardia or even asystole. To discover whether a carotido-sympathetic reflex favors pulmonary edema through dilatation of the capillary vessels or through direct change of their permeability²² we used vasodilator drugs (sodium nitrite, aminophylline). Sodium nitrite had a moderately beneficial effect. This fact, however, cannot either favor or disfavor any of the two possibilities, because on the one hand, peripheral vasodilation decreases the venous return and may prevent the edema; on the other hand, the pulmonary vasodilator action may increase the severity of the edema. The same may be said about pitressin, which decreased permeability but produced harmful results. The favorable action of curare is explained by the depressant effect of this drug on the brain centers and on the ganglia. That curare has this action is confirmed by the experiments in which the combination of curare with prostigmine gave definitely better results than the use of curare alone.

The actions of physostigmine and prostigmine, which have been discussed at length can be explained only by their depressant effect on the ganglia,²⁴ on the spinal cord,^{35, 36} and on the brain^{24, 25} and not by any cardiac or vascular effect.

Digitalis and digitalis-like glycosides were tried in order to study the suggestion of French authors that they might be useful.³³ The slightly beneficial action of strophanthin may be explained by the reduction in the size of the distended ventricles and by the consequent decreased stimulation of cardiac receptors. If cardiac failure were the cause of the type of experimental edema of the lungs which we are studying, the result would have been much more striking.

The pharmacologic experiments reported here confirm our previous interpretation³ of the acute pulmonary edema brought about by our standard method. We believe that this general conclusion, which had been foreshadowed by results of experiments on pulmonary edema caused by adrenalin,⁵ ligation of the aortic arch,⁶ venous infusion,^{7, 8} and suboccipital injection,³⁰ should now definitely focus the attention of students of pulmonary edema upon the nervous system and not upon the myocardium. That either irritation of the myocardium (coronary occlusion), or distention of the heart cavities (heart failure, hyper-

tension) may be one of the causes of pulmonary edema cannot be denied, but we feel that either of these phenomena is secondary to the distention of the large arterial vessels as a cause of reflexes which favor acute edema of the lungs. We should like to emphasize the word "favors." For the occurrence of pulmonary edema a condition of distention of the lung capillaries is essential. This distention is caused by the energetic work of both ventricles, as Sahli and Kotowsechikow have ascertained, and requires high arterial pressure and/or high venous return, as Starling has demonstrated. On this condition, an acute reflex increase of permeability may be superimposed which will lead to paroxysmal edema. Any factor decreasing either the arterial pressure or the venous return will act against the possibility of the edema. Factors leading to a decreased distention of either the ventricular cavities or the arteries containing pressoreceptors will produce the same result. Any depressing effect either on the sensitive receptors, on the nerve centers, or on the autonomic pathways of the reflexes will also help prevent the edema.

General Considerations on the Prevention and the Therapeutics of Pulmonary Edema.—In our systematic study of the effect of drugs on experimental pulmonary edema the following drugs were found to be useful: (1) hypnotics; (2) prostigmine, in combination with either curare and atropine or morphine and atropine; (3) drugs inhibiting the sympathetic system; and (4) less constant results were obtained with local anesthetics (novocaine) or trasentine.

That hypnotics would exert a beneficial action was foreseen from the results of previous experimental and clinical studies. Chloral hydrate alone and in combination with morphine seems to be the most promising for clinical applications. The action of prostigmine in combination with either morphine or curare has been described for the first time and may give favorable results in clinical applications. Novocaine may exert a favorable action, but should not be used in large doses. Trasentine deserves further study and may prove useful. Aminophylline, mercurial diuretics, and papaverine may be of general help in preventing edema, but proved ineffective if used in the imminence of an attack. Digitalis and strophanthin should also not be counted upon in the treatment of a paroxysmal attack of pulmonary edema. The following may be said of the clinical application of the two main groups of beneficial drugs: (a) Hypnotics may be used by intravenous injection, since their application by this route has been already tried both in normal individuals³⁹ and in clinical cases of pulmonary edema.⁴ (b) Prostigmine and allied drugs should be tried first by subcutaneous injection. Intravenous administration may be superior, but should not be tried until it has been seen that possible secondary effects (bradycardia, bronchospasm, etc.) are not harmful.

SUMMARY

1. A systematic study of various drugs has been made in the treatment of acute experimental pulmonary edema caused by the rapid intracarotid infusion of physiologic salt solution.

2. The following drugs conferred protective effects and tended to prevent the development of edema:

- a. The best results were obtained by hypnotics (phenobarbital, barbital, chloral hydrate) and by combination of any one of the hypnotics with morphine.
- b. A combination of prostigmine with either atropine and curare or atropine and morphine also gave excellent results.
- c. Sympatholytic drugs (ergotamine, 883 F), novocaine, and trasentine gave less constant results.
- d. Vasodilators and drugs stimulating the myocardium only occasionally gave good results.
- e. Atropine, adrenalin, and pitressin definitely made the edema of the lungs worse.

3. Observations on the pathogenesis of acute pulmonary edema caused by the method of rapid intracarotid infusions are drawn from the reported pharmacologic studies. Attention is called to the important part that the central nervous system plays in the syndrome and to reflexes leading to an acute increase of capillary permeability of the lungs.

4. Therapeutic considerations are drawn from the reported experiments.

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THE COINCIDENCE OF AURICULAR FIBRILLATION AND BACTERIAL ENDOCARDITIS

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THE belief that bacterial endocarditis and auricular fibrillation rarely co-exist seems to be almost universal. Many cardiologists believe that bacterial endocarditis practically never develops in the presence of auricular fibrillation. It is the purpose of this paper to study the basis for this belief and to offer a possible explanation why auricular fibrillation occurs less frequently with bacterial endocarditis than with rheumatic heart disease. Those who contend that auricular fibrillation and bacterial endocarditis are rarely encountered together need not look far for support.

In 1923, Blumer¹ found four instances of auricular fibrillation among 301 patients with subacute bacterial endocarditis. In this study he noted, "These figures, however, are probably misleading, for many cases were recorded long before modern methods of pulse study were in vogue." In 1926, Thayer² reported that in 60 fatal cases of subacute bacterial endocarditis (streptococci), in the main the result of myocardial insufficiency, four cases of auricular fibrillation were encountered. In neither of the above studies was there any mention of one process' developing before the other.

In 1927, Rothschild, Sacks, and Libman³ reported a study of 123 patients with subacute bacterial endocarditis, 61 of whom had had electrocardiograms made. Among these 61 patients, auricular fibrillation was encountered in four. There was no evidence that auricular fibrillation was present in any of the 62 patients for whom no electrocardiograms were made. In one of the four cases with fibrillation the rhythm had been normal until three days before death. This was the only instance in the group in which fibrillation developed in an active case. In the other three patients, fibrillation developed in the bacteria-free stage. Basing their opinion upon the occurrence of auricular fibrillation in three of fourteen patients in the bacteria-free stage of bacterial endocarditis, they stated that the coexistence of these two pathologic processes was relatively common. These authors noted that, even in the presence of heart failure, the patients generally retain a normal rhythm. They also approached the problem from another aspect. In a study of 200 patients with auricular fibrillation selected at random, they found that none had, or developed, subacute bacterial endocarditis. They concluded, "The observation that auricular fibrillation and active subacute bacterial endocarditis are mutually exclusive (save in an exceptional instance) is of diagnostic value."

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In 1932, Fulton and Levine⁴ reported that in a study of 111 patients with subacute bacterial endocarditis, auricular fibrillation was found only in one instance, where it developed as a terminal event. Of these 111 cases, 84 were hospital patients, and electrocardiograms were made on 62. They stated, "The inference to be drawn is that the heart remains essentially regular in subacute bacterial endocarditis, and, furthermore, if a patient had auricular fibrillation it is extremely unlikely that he had or ever will develop subacute bacterial endocarditis."

In 1933, Laws and Levine⁵ noted that two of 43 patients with subacute bacterial endocarditis had auricular fibrillation. In one of these the auricular fibrillation was present before the onset of the subacute bacterial endocarditis, and in the other it occurred as a terminal event. In 1935, Segal⁶ reported 192 cases of subacute and acute bacterial endocarditis. In this group, auricular fibrillation was encountered five times. In only one case did the auricular fibrillation precede the onset of the bacterial endocarditis. Finally, in 1941, Christian⁷ reported that, in 150 cases of *Streptococcus viridans* endocarditis, only four patients were observed to develop auricular fibrillation.

In summarizing these seven studies, one finds that they include a total of 980 cases of bacterial endocarditis. In the total group, auricular fibrillation was present in 24 cases (2.45 per cent). Of these 24 patients with auricular fibrillation, in 11 fibrillation definitely began after the onset of bacterial endocarditis, in two auricular fibrillation definitely antedated the onset of bacterial endocarditis, and in 11 patients no mention was made of one process' occurring before the other.

SOURCE AND ANALYSIS OF MATERIAL

This paper is based upon a study of 286 cases of bacterial endocarditis. These all came to autopsy and were taken from the University of Minnesota Hospitals, Ancker Hospital of St. Paul, Minneapolis General Hospital, and various other hospitals in Minneapolis and St. Paul (Table I). In this series of 286 patients, 36 examples of auricular fibrillation were encountered (12.59 per cent).

TABLE I. SOURCES OF TWO HUNDRED AND EIGHTY-SIX CASES OF BACTERIAL ENDOCARDITIS AND PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION

HOSPITAL	CASES OF BACTERIAL ENDOCARDITIS	CASES OF AURICULAR FIBRILLATION	PERCENTAGE OF COINCIDENCE
University of Minnesota	62	5	8.06
Ancker	64	8	12.50
Minneapolis General	70	11	12.55
Others	90	12	13.33

Because the reports on many of the 90 cases from "Other Hospitals" were not complete, further analysis in this study has been confined to the 196 cases from the first three hospitals listed in Table I.

The distribution of the 196 cases of bacterial endocarditis in the various age groups, with the frequency of auricular fibrillation, is shown in Table II. Generally speaking, this disease is an affection of the younger age groups.

TABLE II. AGE DISTRIBUTION AND PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION IN ONE HUNDRED AND NINETY-SIX PATIENTS WITH BACTERIAL ENDOCARDITIS

AGE (YRS.)	NUMBER OF CASES OF BACTERIAL ENDOCARDITIS	PERCENTAGE OF TOTAL CASES	NUMBER OF CASES OF AURICULAR FIBRILLATION	PERCENTAGE IN- CIDENCE OF AURICULAR FIBRILLATION
0 to 9	6	3.06	1	16.67
10 to 19	20	10.20	0	0.00
20 to 29	53	27.04	7	12.96
30 to 39	41	20.92	4	9.76
40 to 49	32	16.33	3	9.38
50 to 59	28	14.29	5	17.86
60 to 69	10	5.10	3	33.33
70 to 79	3	1.53	0	0.00
80 to 89	3	1.53	1	33.33

It will be noted that the incidence of bacterial endocarditis reaches its peak in the third decade. The incidence of auricular fibrillation is higher in the older age group, reaching 20.5 per cent after the age of 50 years, as compared with 9.87 per cent up to the age of 50.

The sex incidence showed 88 women and 101 men. Seventy-five per cent of the women with bacterial endocarditis came to autopsy before the age of 40 years, while only 50 per cent of the men so affected were autopsied before this age. This observation would suggest that women develop active bacterial endocarditis at an earlier age.

The combinations of valvular involvement were studied in the 196 cases, and several interesting findings were noted. Table III shows the incidence of bacterial endocarditis and auricular fibrillation in the various combinations of valvular involvement.

TABLE III. THE INCIDENCE OF BACTERIAL ENDOCARDITIS AND AURICULAR FIBRILLATION IN RELATION TO VARIOUS VALVULAR INVOLVEMENTS

VALVES INVOLVED	NUMBER OF CASES OF BACTERIAL ENDOCARDITIS	PERCENTAGE OF CASES OF BACTERIAL ENDOCARDITIS	NUMBER OF CASES OF AURICULAR FIBRILLATION	PERCENTAGE INCIDENCE OF AURICULAR FIBRILLATION
Aortic and mitral	87	44.39	11	12.64
Mitral alone	80	40.82	9	11.25
Aortic alone	18	9.18	3	16.67
Tricuspid, aortic, and mitral	3	1.53	0	0.00
Tricuspid and aortic	1	0.51	0	0.00
Tricuspid, mitral, and pulmonary	1	0.51	0	0.00
Tricuspid alone	3	1.53	0	0.00
No valvular involvement	3	1.53	1	33.33

It is seen that involvement of both aortic and mitral valves on the one hand, and of the mitral valve alone on the other, were about equal. The incidence of auricular fibrillation in both groups was about the same: 12.64 per cent and 11.25 per cent, respectively. It is of especial interest that in the cases in which only the aortic valve was involved the incidence of auricular fibrillation was fully as high as in the cases with mitral involvement alone or combined aortic and mitral valvular involvement. In the patients in whom only the aortic

valve was involved, the mechanism producing auricular fibrillation was presumably based on a relative mitral insufficiency due to left ventricular dilatation.

The single example of auricular fibrillation with no valvular involvement occurred in an 8-year-old boy. This patient had a bacterial endocarditis superimposed on an active rheumatic carditis. The auricular fibrillation developed sometime after the onset of the bacterial endocarditis, but it persisted over a period of three and one-half months, until the death of the child.

Analysis of the Twenty-Four Cases of Auricular Fibrillation.—The fibrillation in 21 patients was persistent; in three it was of the paroxysmal variety. Congestive failure was present in all of the 21 patients with the persistent variety and in one of the three patients with paroxysmal fibrillation.

The following data in regard to the onset and duration of the fibrillation were observed: Of the three patients with paroxysmal auricular fibrillation, one had fibrillation during the thirteen days of hospitalization prior to death, one had fibrillation for the one day of hospitalization before death, and one had two observed paroxysms of fibrillation during thirty-three days of hospitalization prior to death. Of the 21 patients with persistent auricular fibrillation, five definitely developed fibrillation after bacterial endocarditis was present. Ten of the 21 patients showed both fibrillation and bacterial endocarditis at the time of admission, and therefore no statement can be made regarding the occurrence of one process before the other. In six, a persistent auricular fibrillation was definitely present before the bacterial endocarditis developed. These six cases in which auricular fibrillation preceded the onset of bacterial endocarditis are emphasized because of the supposed rarity of this condition. In 18 of the 24 cases of auricular fibrillation, the diagnoses were based on electrocardiographic as well as clinical evidence. Electrocardiograms had been obtained in every case in which auricular fibrillation antedated the onset of bacterial endocarditis.

DISCUSSION

There are differences in the results of this study and of other reported studies in regard to the frequency of the coexistence of auricular fibrillation and bacterial endocarditis. The discrepancy is difficult to explain. This report is based upon the study of consecutive cases taken from the protocols of the three hospitals mentioned. In every instance there was a thorough study of both the pathologic protocols and the hospital charts, and the existence of bacterial endocarditis was confirmed by autopsy.

In comparison with the incidence of auricular fibrillation in rheumatic heart disease which is usually accepted (40 to 53 per cent in the studies of de la Chapelle, Graef, and Rottino,⁸ DeGraff and Lingg,⁹ and Stone and Feil¹⁰), the coincidence of auricular fibrillation and bacterial endocarditis is low. However, in the present study no basis has been found for postulating a protective mechanism on the part of auricular fibrillation against the development of bacterial endocarditis, nor does there seem to be anything to suggest that these two disorders are mutually exclusive. The answer to this problem seems to depend

upon two factors which contribute to the development of auricular fibrillation: the integrity of the myocardium and the duration of the disease affecting the heart.

Congestive heart failure may be taken to be an expression of an inefficient myocardial function. In the 196 cases of bacterial endocarditis, the incidence of congestive failure, as indicated by chronic passive congestion of the liver, was about 40 per cent. However, in the 24 cases with auricular fibrillation 91 per cent showed congestive failure, and in the 21 cases of persistent auricular fibrillation, congestive failure was present in every instance. In their study of rheumatic hearts, de la Chapelle, Graef, and Rottino⁸ found that the incidence of congestive failure was 88 per cent. Thus, in the cases of bacterial endocarditis reported, the percentage incidence of congestive failure is somewhat less than half that found in chronic rheumatic heart disease.

In regard to the duration of rheumatic heart disease, it is accepted that the incidence of auricular fibrillation in heart disease increases with the age of the patients. DeGraff and Lingg,⁹ investigating the course of rheumatic fever in adults, reported that auricular fibrillation "is a late manifestation in rheumatic heart disease." They further stated, "It appears, then, that patients who died of subacute bacterial endocarditis have not had rheumatic heart disease long enough to develop auricular fibrillation; hence, the rare coexistence of the two conditions." Garvin,¹¹ in a study of rheumatic heart disease, concluded that "in fatal rheumatic heart disease, as in fatal hypertension and coronary disease, auricular fibrillation is found in older patients, while a normal cardiac mechanism usually is encountered in younger patients." It was previously mentioned that the greatest number of deaths from bacterial endocarditis was encountered in the age group from 20 to 29 years, and that the general impression was that bacterial endocarditis is a disease of the younger age group. Rheumatic heart disease with congestive failure has its highest incidence in the fourth and fifth decades (Clawson¹²).

That the grade of mitral stenosis is a factor in determining the incidence of auricular fibrillation does not seem to be a conclusion justified by this study; for, as has been previously noted, the coincidence of auricular fibrillation and bacterial endocarditis was about the same whether the mitral valve was involved alone, whether the mitral and aortic valves were both involved, or whether only the aortic valve was involved. Our belief that auricular fibrillation does not depend upon the degree of mitral stenosis is in full agreement with the conclusions of de la Chapelle, Graef, and Rottino⁸ and of Segal.⁶ It seems much more probable that the pathogenesis of auricular fibrillation is more closely related to the myocardial integrity, both physiologic and anatomic, than to the degree of severity of mitral stenosis per se.

The most probable explanation of the fact that auricular fibrillation is present less frequently in bacterial endocarditis than in rheumatic heart disease without bacterial endocarditis is that sepsis intervenes to cause death before the patient with bacterial endocarditis develops auricular fibrillation and congestive failure indicative of severe myocardial failure.

CONCLUSIONS

1. In 286 patients with bacterial endocarditis, 36 examples (12.59 per cent) of auricular fibrillation were encountered.

2. Of the 196 cases in which the character of the fibrillation was analyzed, three were of the paroxysmal type and 21 were of the persistent variety. Of these 21 cases of persistent fibrillation five definitely had an antecedent bacterial endocarditis, in six the auricular fibrillation was definitely present before the onset of bacterial endocarditis, and in 10 both processes were present when our observations began.

3. The incidence of auricular fibrillation was approximately the same irrespective of the type of valvular involvement.

4. The reason that the incidence of auricular fibrillation is significantly lower in bacterial endocarditis than in rheumatic heart disease seems to be that in most cases of bacterial endocarditis fatal sepsis intervenes while the patients are relatively young and before the disturbance of the myocardial integrity becomes severe.

5. The results of this study suggest that the coexistence of auricular fibrillation and bacterial endocarditis is not so rare as was previously supposed, and that one should therefore be cautious in using this point as a diagnostic aid.

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PATHOLOGIC STUDY OF THIRTY-ONE CASES OF SCRUB TYPHUS FEVER WITH ESPECIAL REFERENCE TO THE CARDIOVASCULAR SYSTEM

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SINCE the early phases of the Papuan campaign scrub typhus fever has been recognized as an important problem of military medicine in the Southwest Pacific theater of operations.¹⁻³ Experience with the disease has caused particular concern for the real or hypothetical cardiac complications of the disease. Some support was lent to this attitude by the histopathologic studies of Kouwenaar,⁴ Kouwenaar and Wolff,⁵ and Corbett⁶ and the clinical studies of Lipman, Byron, and Casey.⁷ Other studies, on the contrary, pointed out the possibility of misinterpreting certain physical findings as the result of heart disease⁸ and failed to establish evidence for the existence of chronic heart disease as a sequel of the disease.^{9, 10} From his study of an epidemic of 230 cases in one of the islands of the Southwest Pacific in early 1944, Logue¹¹ stated that "the probability of permanent myocardial damage should be given further consideration." This conclusion was unfortunately misquoted in a popular newsmagazine which stated that "he suspects that all have permanent heart damage." Personal interviews with many medical officers throughout this area have shown that this bogey still persists. It seemed worth while, therefore, to examine a representative sample of pathologic material, focusing attention upon any abnormalities of the cardiovascular system.

METHODS AND MATERIAL

The material for this study comprises the gross and microscopic findings of thirty-one cases of scrub typhus fever autopsied at the Third Medical Laboratory during the year 1944 and made available to me through the courtesy of Captain George P. Smith. The cases included in the study have not been previously reported. The patients ranged in age from 19 to 44 years with a mean age of 24 years (see Table I). Death occurred in from six to twenty-four days after the onset of the disease. The mean duration of the illness was thirteen days. More than half of the deaths occurred between the twelfth and fifteenth days.

Excepting the data substantiating the clinical diagnosis, practically all of the material of this study was derived from the gross autopsy findings and microscopic examination of the tissues. In all thirty-one cases the diagnosis of scrub typhus fever was well established. Every record described regional and generalized lymphadenopathy and a rash, and all but one described a characteristic eschar. The patients' sera agglutinated the OX-Kingsbury strain of the *proteus* bacillus in significant titer in nineteen cases, and in nine cases the

OX-K agglutination could not be carried out. Table I is a consolidation of much of the essential data of this study. The severity of the changes is graded as follows: +=mild, ++=moderate, +++=severe, and ++++=very severe.

PATHOLOGIC CHANGES IN THE HEART AND OTHER ORGANS

I. The Heart.—The hearts ranged in weight from 260 to 500 grams; the mean weight was 330 grams. In four cases the consistency was firm and the color was rusty red or dark mahogany brown. In 27 cases the heart was pale, soft, flabby, or slightly friable. Although two hearts contained small atheromatous plaques in the proximal portions of the coronary arteries, in all cases these vessels were widely patent throughout. In every instance the valves were free, delicate, and competent, and the measurements of the valve rings were normal. In 22 cases there were subepicardial petechial hemorrhages, and in two cases there were subendocardial petechial hemorrhages. In only one case was there a macroscopic hemorrhage into the heart muscle proper.

In six cases the microscopic appearance of the heart was perfectly normal and compact; in twenty-five, microscopic changes were observed. These were located principally in the myocardium, but in 16 cases there were also epicardial or endocardial changes. In five cases the myocardium seemed loose, frayed, and lacy, the muscle fibers being separated either by a thin fibrin network or an inflammatory exudate. This consisted of lymphocytes, plasma cells, and large mononuclear cells, some of which had eosinophilic cytoplasm and somewhat vesicular nuclei usually containing nucleoli. In a few cases there was also a sprinkling of polymorphonuclear leucocytes. This type of exudate was distributed diffusely in the endomyocardial spaces in four cases and as a cuff around blood vessels in seven; in 14 cases there were both a perivascular and an interstitial distribution. As Table I shows, the degree of this reaction was slight in 11 instances, moderate in six, severe in four, and very severe in four. In 13 cases there was a slight to moderate exudation of similar cells into the endocardium which might be slightly thickened, and in 16 cases the cells were found in the fibrous or fatty tissue of the epicardium. Fig. 1 shows an example of this type of reaction. In both locations the reaction was generally continuous with an identical reaction in the contiguous myocardium, but in a few instances the epicardial exudate was perivascular in distribution.

Of the twenty-five cases showing carditis, thirteen showed intact heart muscle fibers throughout with normal nuclear and cytoplasmic structure, but in twelve cases the cytoplasm had undergone minor degrees of hyaline degeneration, loss or indistinctness of striation, vacuolization of the cytoplasm, or fragmentation of the muscle fibers. Usually this muscle fiber necrosis was restricted to the cytoplasm but in two cases nuclear degeneration was also observed. An extreme degree of this type of myocardial degeneration is illustrated in Fig. 2. In one part of the field an intact muscle fiber is seen, and on the opposite side a fiber shows hyaline degeneration, vacuolation, and fragmentation. The cytoplasmic changes, when present, were most pronounced in the regions of focal exudation. In two cases this reaction involved the subendocardial layers of the

TABLE I. CARDIIS, PNEUMONIA, AND CONGESTIVE FAILURE IN SCURB TYPHUS FEVER

CASE	AGE (YRS.)	DURATION IN DAYS	HEART		LUNGS			LIVER		KIDNEYS			ASCITIC FLUID (C.C.)	EDEMA	PLEURAL FLUID RIGHT (C.C.)		PLEURAL FLUID LEFT (C.C.)		PERI- CARDIAL FLUID (C.C.)
			WEIGHT GM.	CARDI- TIS	WEIGHT (GM.)		PNEU- MONIA	CONGES- TION	WEIGHT GM.	CONGES- TION	WEIGHT (GM.)				RIGHT	LEFT			
					RIGHT	LEFT					RIGHT	LEFT							
1	-	16	395	++++	1,130	960	+	+++	2,680	+	230	-	500	0	0	200	100		
2	22	12	500	++++	950	900	++	++	1,900	+	285	290	0	0	1,500	1,500	300		
3	24	12	380	++++	850	775	++	++	2,630	++	235	225	500	0	0	0	50		
4	37	24	270	++++	1,300	1,200	++++	++	1,900	0	220	220	0	0	0	0	0		
5	36	15	350	++++	1,250	1,050	++	++	1,950	0	290	265	0	0	0	0	0		
6	30	14	370	++++	1,215	1,100	++	++	2,026	0	240	225	0	0	0	0	30		
7	30	15	330	++++	1,000	885	++	++	1,880	+	200	235	0	0	0	0	30		
8	22	16	275	++	1,200	900	++	++	1,800	0	150	150	0	0	0	0	0		
9	30	18	450	++	1,400	-	++	++	1,800	++	300	200	700	++	1,500	1,500	200		
10	23	13	270	++	1,030	910	++	++	2,050	++	225	245	0	0	0	400	50		
11	22	17	260	++	800	650	++	++	-	0	265	245	0	0	0	0	0		
12	44	7	310	++	1,400	1,150	++	++	2,200	+	170	170	0	0	0	0	0		
13	21	15	415	++	735	910	++	++	2,230	++	250	300	300	++	400	400	150		
14	43	13	340	++	700	700	++	++	2,000	0	245	285	0	0	0	0	0		
15	32	-	325	+	1,100	950	++	++	2,100	0	210	190	0	0	0	0	0		
16	20	20	405	+	545	545	+	++	2,200	+	225	290	0	0	0	0	0		
17	19	10	300	+	900	850	++	++	1,850	0	-	-	500	0	250	250	25		
18	-	14	290	+	1,200	1,100	++	++	2,500	0	260	260	75	0	0	0	60		
19	27	12	315	+	1,180	750	++	++	1,700	++	190	190	0	0	0	0	50		
20	24	9	315	+	950	750	++	++	2,075	++	240	250	200	0	500	500	-		
21	22	8	335	+	1,265	1,065	0	+	1,950	++	185	230	0	0	0	0	50		
22	25	9	390	+	1,200	950	++	++	1,900	++	210	190	500	0	500	500	100		
23	22	12	360	+	1,260	1,230	++	++	2,290	++	180	200	700	+	600	600	30		
24	-	14	380	+	790	745	++	++	2,410	++	230	230	800	+	1,000	1,000	100		
25	-	-	300	+	750	750	++	++	2,400	++	-	-	100	0	250	250	-		
26	-	12	290	0	900	850	++	++	1,850	0	190	200	1,500	0	50	50	0		
27	22	13	275	+	1,300	700	++	++	2,350	0	210	190	250	0	250	0	0		
28	27	10	355	0	955	885	++	++	1,910	0	200	180	100	0	0	0	0		
29	21	6	280	0	500	450	+	+	2,000	+	225	250	0	+	0	0	30		
30	-	12	280	0	600	670	++	++	2,300	0	190	190	0	0	0	0	50		
31	26	14	275	0	600	550	++	0	2,300	++	-	-	0	0	0	0	0		

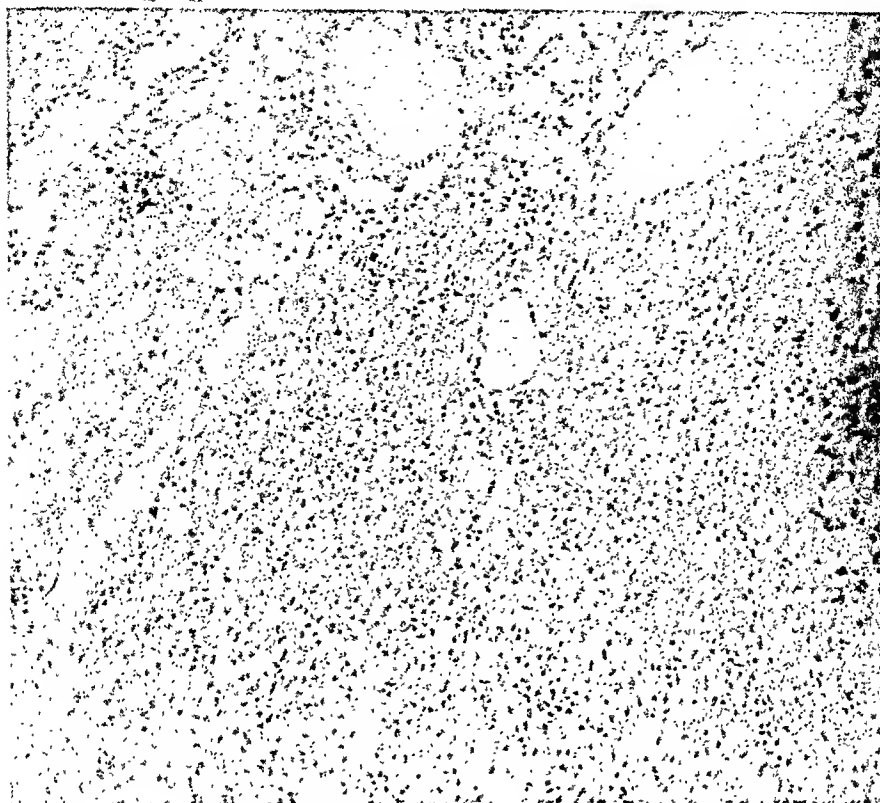


Fig. 1.—Case 9. Pericardial infiltration in scrub typhus fever. ($\times 20$.) For their courtesy and cooperation the author is indebted to Colonel Dwight M. Kuhns and Sergeant Dave Brunk of the Nineteenth Medical General Laboratory where the photomicrographs illustrated in this article were made.

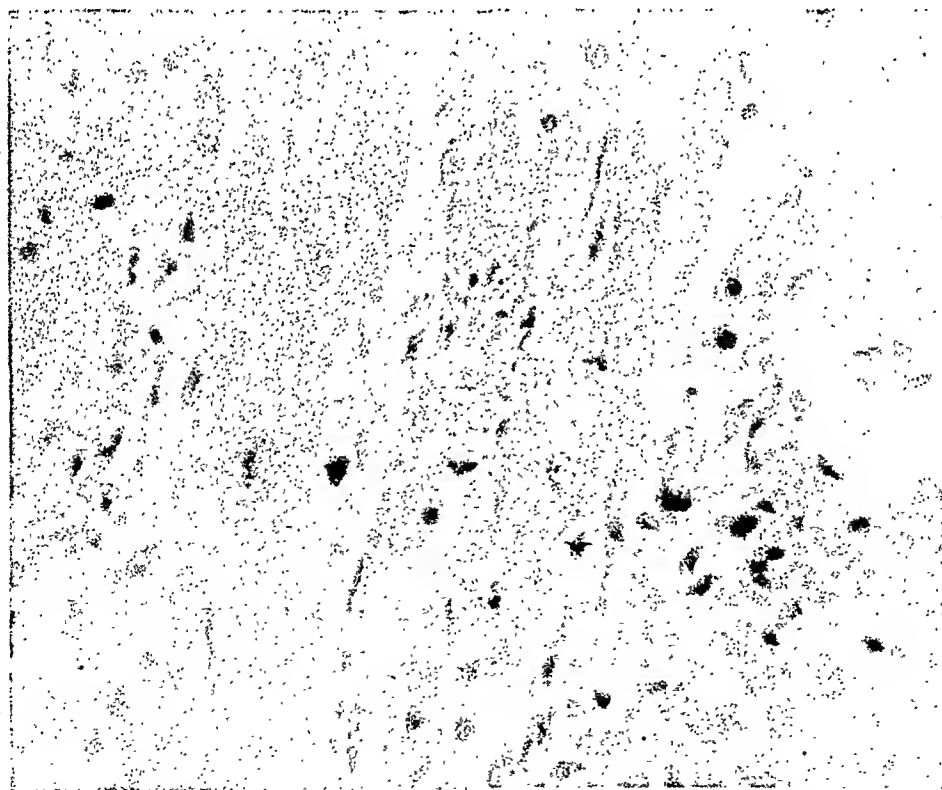


Fig. 2.—Case 2. Myocardial necrosis in scrub typhus. Note the relatively intact muscle fiber on the left in contrast to the fibers on the right which show hyaline degeneration, vacuolation, and dissolution. ($\times 950$.)

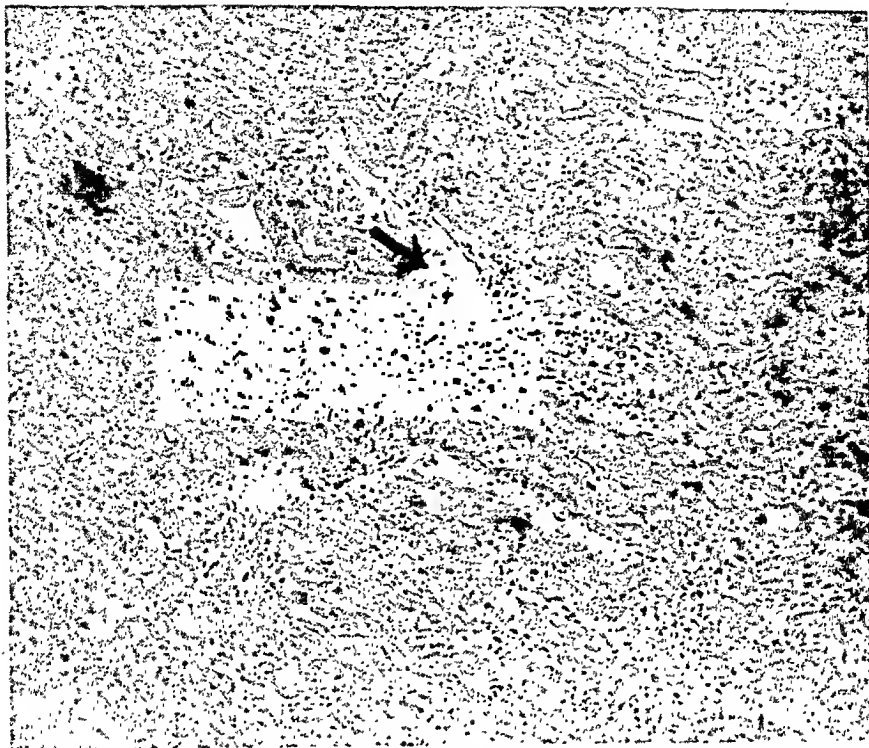


Fig. 3.—Case 8. Endothelial proliferation in one of the smaller vessels of the heart. Note the focal perivascular infiltration. Arrow indicates an area of heaping up of the endothelial cells. ($\times 20$.)

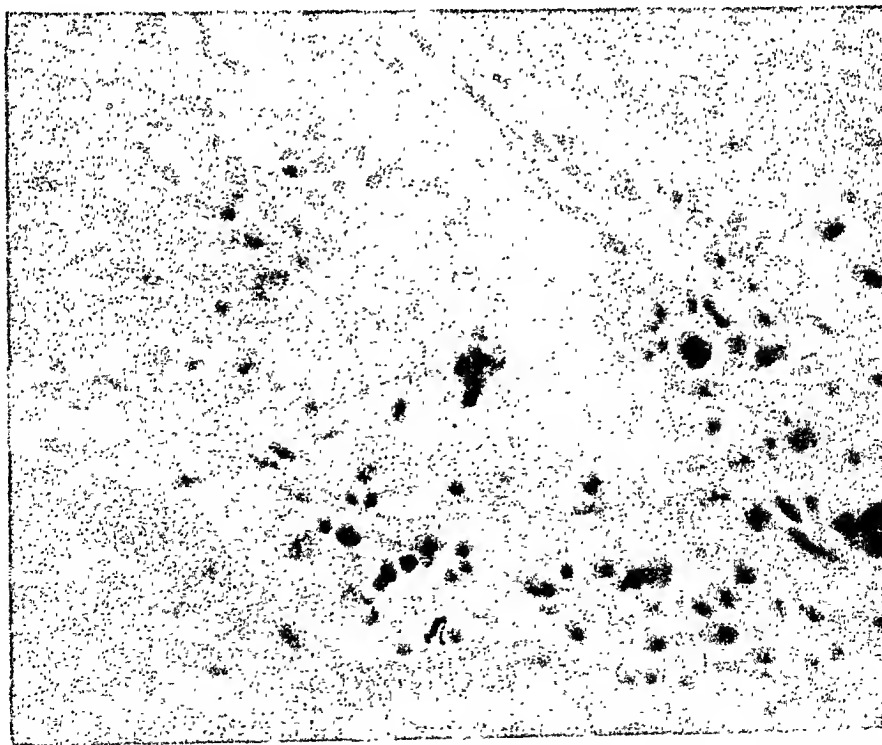


Fig. 4.—Case 8. Same section under higher magnification. Shows endothelial hyperplasia more clearly. ($\times 440$.)

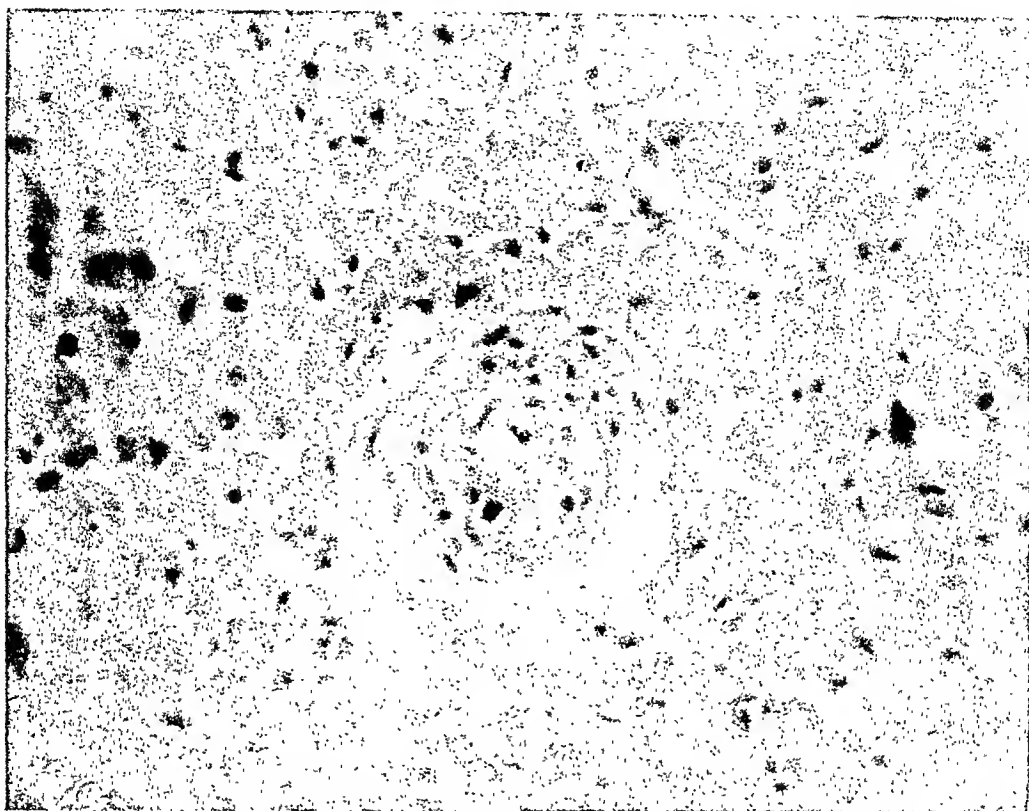


Fig. 5.—Case 14. Eccentric endothelial hyperplasia in a larger blood vessel in one of the papillary muscles of the left ventricle. (X440.)

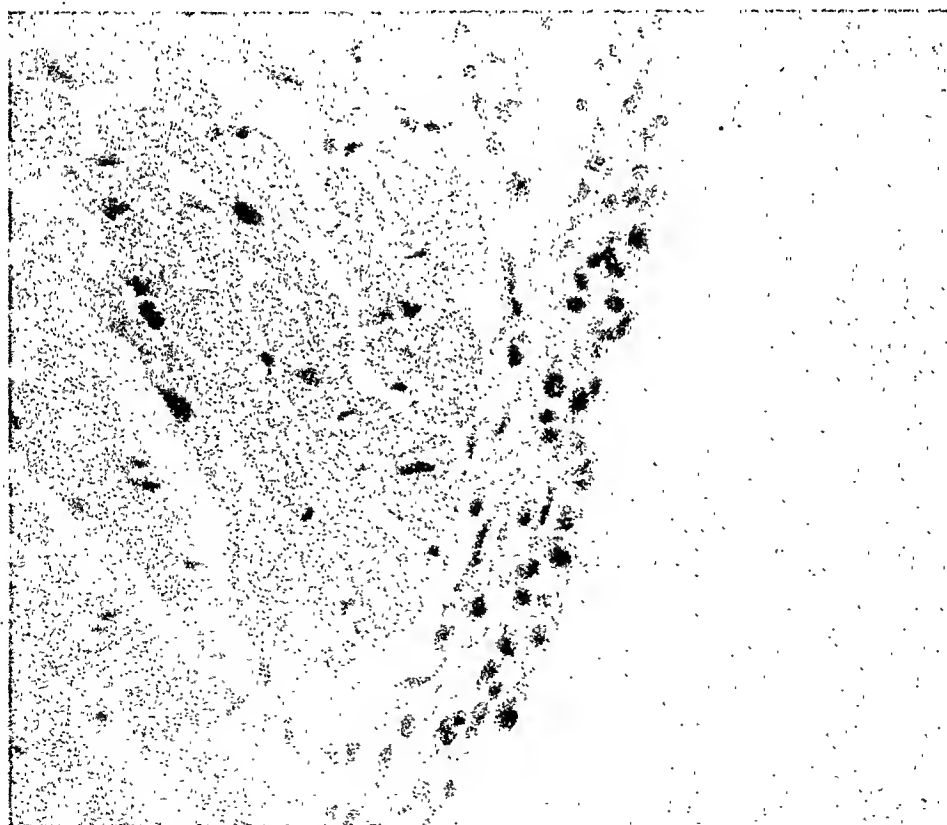


Fig. 6.—Case 3. Endocardial hyperplasia in the left ventricle. Whereas this layer should consist of a flat ribbon of spindle-shaped endothelial cells, the cells are heaped up and almost cuboidal in shape. (X440.)

myocardium. Though a planned systematic investigation of the conducting tissues of the heart was not made, inflammatory reactions of slight degree were observed in the Purkinje tissue of the papillary muscles in two cases. Evidence of fibrous tissue replacement of muscle fibers could not be established clearly.

The endothelium of the smaller blood vessels in the regions of focal perivascular exudation often showed proliferative changes (see Figs. 3, 4, and 5). Such piling up of the endothelium was noted in nine cases. No definite endothelial necroses could be demonstrated. Similar proliferative endovascular changes were not observed in the larger coronary vessels or in the intermediate-sized vessels lying in the fibrous tissue septa of the myocardium. In six cases the endothelium of the left ventricle was thickened by a similar mild endothelial hyperplasia (see Fig. 6).

II. The Lungs.—Except in seven instances in which there were old pleural adhesions and in three cases in which there were recent fibrinous adhesions on the lateral or diaphragmatic surfaces of one or both lower lobes, the pleural surfaces of both lungs were smooth, free, and glistening, showing, in seven cases, a varying number of subpleural hemorrhages. The right lungs varied in weight from 500 to 1,400 grams, the mean weight being 1,000 grams. The corresponding weights for the left lungs were 450, 1,230, and 885 grams, respectively. In most instances the lower lobe of each lung was either uniformly or spottily solid in consistency, lacking normal crepitation. In two cases, in addition to the involvement of the lower lobes, there was similar solidification of the middle lobe of the right lung and in two cases, of an upper lobe as well. In only two cases was the consolidation more pronounced in the upper than in the lower lobes. The cut surfaces of these more solid portions of the lungs were moist and either homogeneously deep purple or mottled, showing differences in color ranging from salmon pink through rusty red to plum purple. On scraping, the cut surface of the involved lung tissue exuded a frothy pink or red material.

In three cases there were small, hard, sharply demarcated grayish red raised areas, roughly lobular in distribution which appeared to be pulmonary infarcts. The protocols contained no description of the dissection of the pulmonary arteries or veins.

With one exception every case in this series showed some degree of inflammatory reaction in the lungs on microscopic examination. The severity of those changes is shown in Table I. The inflammatory reaction consisted of intra-alveolar and interstitial exudation of lymphocytes, plasma cells, and large mononuclear cells.

In seven cases in which the illness was of more than average duration there was a varying admixture of polymorphonuclear leucocytes in the exudate. This reaction was usually heaviest in the region of bronchioles and in such instances the bronchioles likewise contained a suppurative type of exudate. Fibrin deposition, dissolution of lung tissue, and degenerated cocci were often noted in such areas. In three cases the exudate was predominantly polymorphonuclear. These changes were regarded as evidences of secondary bacterial infection.

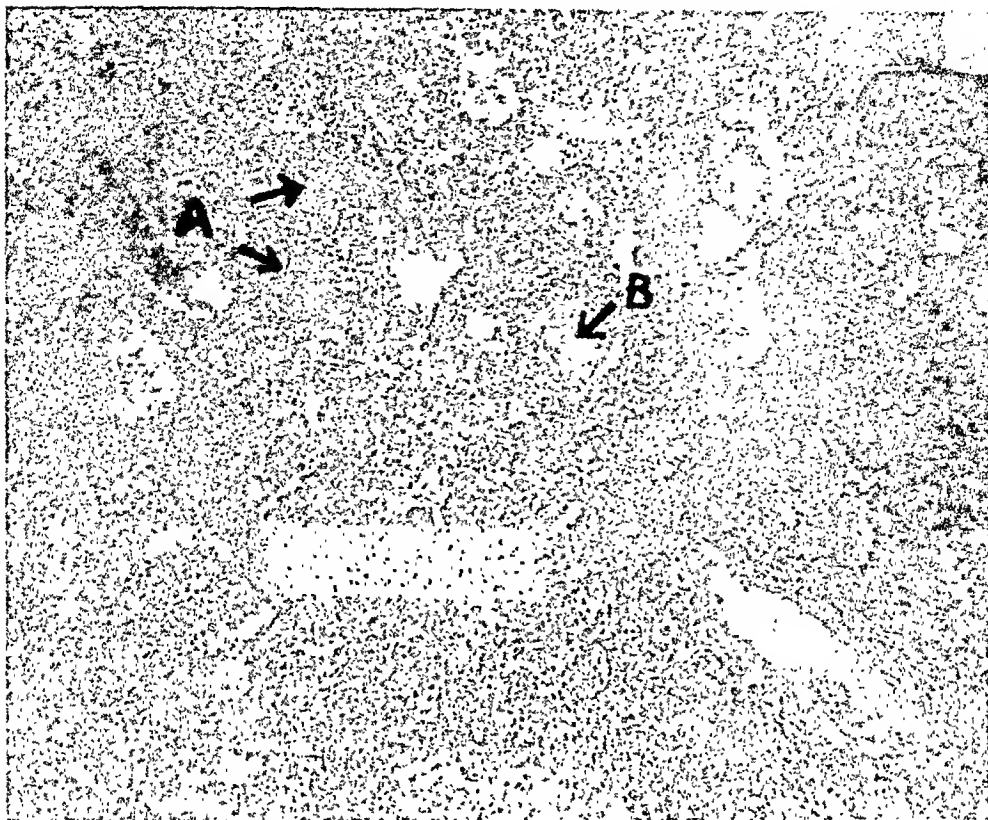


Fig. 7.—Case 13. Severe pneumonic infiltration showing mononuclear type of exudate, hyaline degeneration of alveolar epithelium (A) and the presence of "edema fluid" in some of alveoli (B). (X20.)

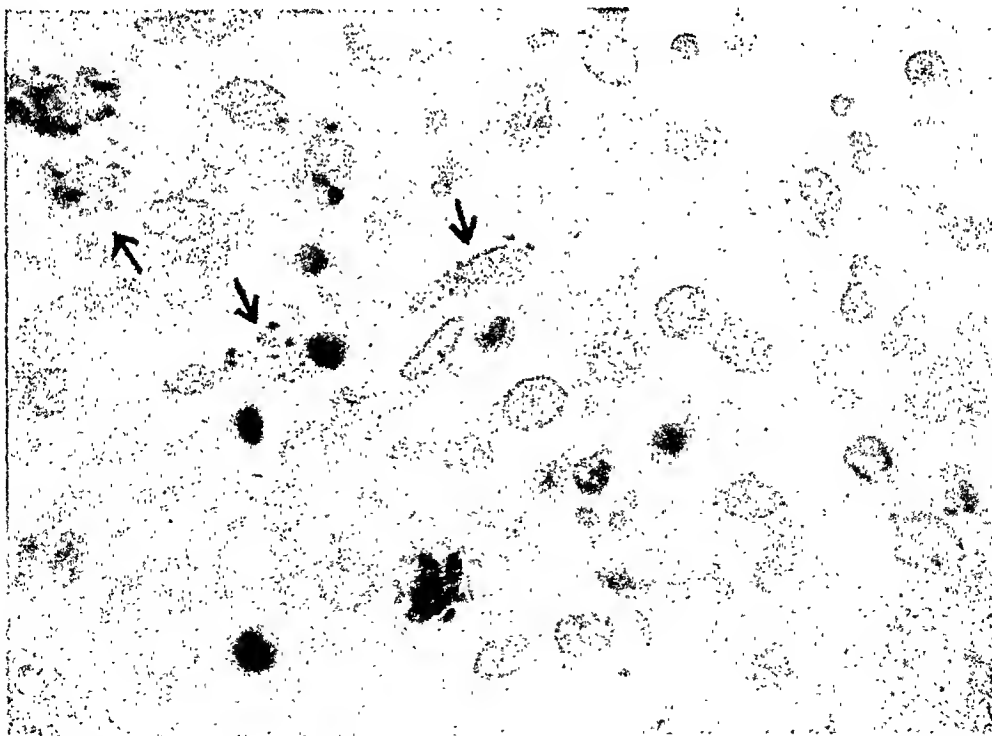


Fig. 8.—Case 22. Characteristic cellular exudate in lung. Note lymphocytes, plasma cells, mononuclear cells, extravasated erythrocytes, and "heart failure" cells, the latter indicated by arrows. (X950.)

The alveolar walls were well maintained in some cases but very indistinct in others. They often were completely ruptured and, in a few instances, were replaced by hyaline, (see Fig. 7). Marked atelectasis was noted in some portions of the lungs in most cases. The blood vessels of the supporting tissue of the lung and of the alveolar walls were moderately to markedly congested and were surrounded by mild to moderate round cell infiltration. In heavily congested areas large numbers of erythrocytes had broken into the alveolar spaces; occasionally they filled many contiguous alveoli. In regions of hemorrhage many large mononuclear cells, much larger than those already described as part of the cellular exudate and containing granules of golden pigment material, were observed in the alveoli. These would correspond to the "heart failure cells" of the older pathology (see Fig. 8).

In regions adjacent to areas showing moderate or heavy inflammation, the exudate was thinner and a pale pink homogenous material filled the alveoli in whole or part. This was interpreted as "edema fluid." The combination of hyaline degeneration of the alveolar epithelium, hemorrhagic edema, and mononuclear exudation gave an appearance reminiscent of that observed in the pandemic of influenza in 1918. In none of the blood vessels of the lung were ante-mortem thrombi seen.

III. The Liver.—In eight cases in this series the liver extended below the right costal margin from 2 to 8 cm., as measured in the midclavicular line. The liver edge was described as rounded in nine cases and sharp in the remaining twenty-two cases. The organs varied from 1,700 to 2,680 grams in weight, the mean weight in the series being 2,050 grams. The surface was always smooth and glistening, but it varied in color from pale yellow (rare) to dark brown and, in three cases, it showed subcapsular hemorrhages. The cut surface showed a characteristic "nutmeg" appearance in four cases and "engorgement" in an additional six cases.

The principal microscopie picture in eighteen cases was that of congestion of the central veins and hepatic sinusoids with vacuolation, granular degeneration, pigment deposition, and necrosis of the central cells of the hepatic lobules. In the remaining thirteen cases there was no congestion. In four of the eighteen cases showing hepatic congestion there was no evidence of accumulations of fluid elsewhere; in the remaining fourteen, edema of the feet or accumulations of fluid in one or more of the serous cavities of the body were noted. Conversely, eighteen of the nineteen patients in the entire series with anasarca showed hepatic congestion of some degree. In fourteen of the eighteen cases with hepatic congestion there was some degree of myocarditis; in the remaining four there was none. Conversely, of twenty-five cases in which there was some degree of myocarditis, fifteen showed hepatic congestion and ten showed none. Hence, although congestion of the liver occurred parallel with congestion elsewhere, carditis was associated with congestion of the liver in only about three-fifths of the cases.

In twenty-eight cases there was some increase in the cellular infiltration of the periportal spaces. The cells in this region were of the same type as those

described in the heart and comprised lymphocytes, plasma cells, and mononuclear cells. In fourteen cases the cellular infiltration was associated with some degree of peripheral necrosis. In six cases there was noted a focal type of necrosis, of irregular distribution, with a light to moderate focal inflammatory reaction of the same cellular type as that described previously. In several cases there were various degrees of congestion, periportal inflammation, and central, peripheral, or focal necrosis in the same individual.

IV. The Kidneys.—The gross appearance of the kidneys was not remarkable. They varied in weight from 180 to 300 grams, the mean weight being 225 grams. In seventeen cases the cut surface of the kidneys was normal pink. In seven it was pale pink and in seven deep purplish red. In seven there were hemorrhages into the mucosa of the renal pelvis. One kidney showed several small subcapsular hemorrhages and a few hemorrhagic areas in the cortex.

In twenty-two cases the principal microscopic feature was congestion of the renal blood vessels with erythrocytes, which appeared most marked in the pyramidal portion but occasionally was seen in the glomeruli as well. In nine of the thirty-one cases studied there was no congestion. As with the liver, there was a high degree of correlation between renal congestion and the presence of myocarditis, and usually, renal congestion occurred parallel with hepatic congestion. Viewed from the other angle, nineteen of the twenty-five cases in the series showing myocarditis had an associated renal congestion whereas six had none.

Multiple small hemorrhages were noted among the straight tubules in sixteen cases and in Bowman's capsule in one. In fifteen cases there was an inflammatory exudate in the renal parenchyma, usually in the medulla, consisting of lymphocytes, plasma cells, and mononuclear cells. In about half of these cases the interstitial exudate was diffuse. In the other half the exudate was focal in distribution and associated with focal necrosis of the regional tubular epithelial cells. Post-mortem autolysis of varying degrees was noted in the tubules in twenty cases.

V. The Suprarenal Glands.—Excepting small hemorrhages in the fascial tissues surrounding the gland (in two cases) or into the adrenal parenchyma (in two cases) and a deep red discoloration of the medulla (in six cases) the gross appearance of the external and cut sections of the suprarenal glands was quite normal. In thirteen cases vascular congestion was noted. This was most prominent in the medulla but extended variable distances into the adrenal cords. Extravasation of blood into the adrenal cortex was seen in a few cases (Fig. 9). Focal necroses and inflammatory reactions of the same type as those described in other organs were seen in six cases, occasionally medullary but usually cortical in location (Fig. 10).

Congestive, hemorrhagic, and inflammatory changes, therefore, were not as frequently observed in the suprarenal glands as in the kidneys. But, with two exceptions, when present they were associated with some degree of carditis.

VI. The Brain and Meninges.—Although minor cerebral changes occurred in the majority of cases in only ten were they considered extensive or severe enough to be important. In two cases the cerebral convolutions were described

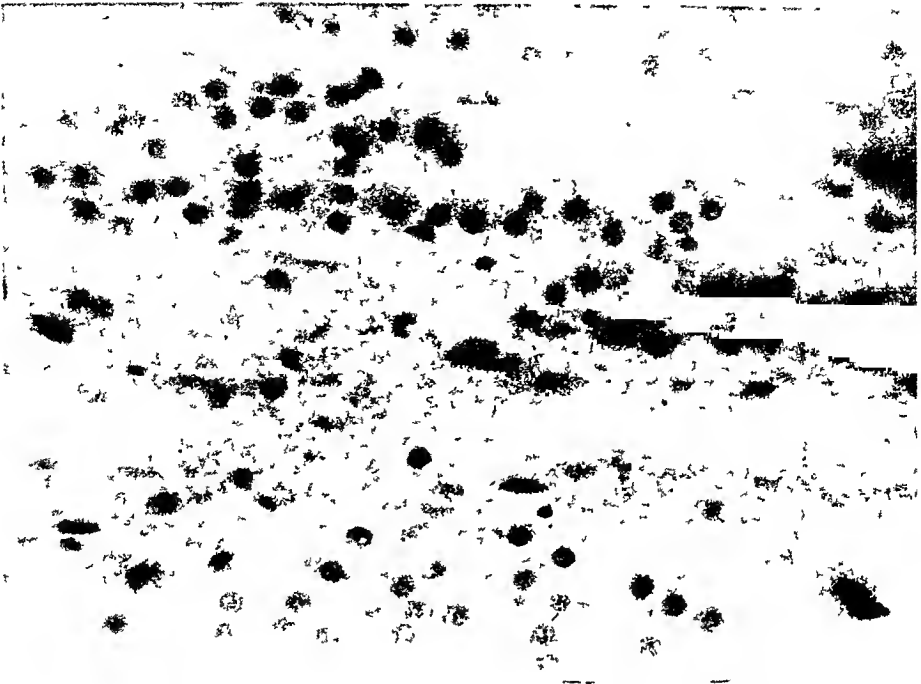


Fig. 9.—Case 3. Hemorrhage in adrenal cortex. ($\times 440$.)



Fig. 10.—Case 1. Focal necrosis and infiltration in adrenal cortex. ($\times 20$.)

as flattened. The leptomeninges were congested in eight cases. In eleven cases petechial hemorrhages were seen with the naked eye on the cut surface of the brain.

A surprising microscopic feature was the infiltration noted in the meninges. These contained a diffuse (in 12 cases) or focal (in three cases) large and small mononuclear cell exudate. In fourteen cases there were focal lesions consisting either of a perivascular lymphocytic and mononuclear cell exudate or dense clusters of microglial cells (the so-called "typhus nodules"). In eleven cases these nodules were more or less uniformly distributed throughout the brain substance and in three only in certain regions of the brain. In eight cases microscopic hemorrhages were observed in the brain substance. Thromboses were never encountered.

CONGESTIVE HEART FAILURE

Edema of the ankles or accumulations of fluid in at least one of the serous spaces of the body was noted in twenty-three cases in this series. All but two of these were associated with some degree of carditis. In all cases the anasarca was associated with visceral congestion. On the contrary, of 25 cases showing carditis, 18 showed some anasarca while seven did not. Ascitic fluid, noted in 14 cases, varied in volume from 50 to 1,500 c.c., the mean being 500 cubic centimeters. Hydropericardium was noted in 13 cases, the pericardial fluid was estimated at between 50 and 300 c.c., mean volume being 75 cubic centimeters. Eleven cases showed right, and twelve left, hydrothorax. The volume of pleural fluid varied from 50 to 1,500 c.c. with a mean of 500 cubic centimeters. Edema of the feet or ankles was noted in eight cases.

HEMORRHAGIC PHENOMENA IN SCRUB TYPHUS

A notable feature in the present series was the frequency of hemorrhagic manifestations. Subcapsular hemorrhage of the liver, subcapsular, parenchymatous, or submucous hemorrhage of the kidney, hemorrhage into the pleural and pericardial membranes, and hemorrhage into the suprarenal gland, lung, and brain have already been described. Hemorrhages were also observed in the mucosa of the gastrointestinal tract in ten cases. These were usually located in the upper portion, but in two cases the colon was involved as well. One of these patients passed gross blood in his stools. One patient had a severe hemoptysis; microscopic examination in this case showed large hemorrhages into the pulmonary alveoli. Seven patients had epistaxes; in three of these the bleeding was severe enough to require packing of the nose. One patient had a hemorrhage into the submucosa of the urinary bladder. Five had hemorrhages into the sclerae. One of these patients who had several subconjunctival hemorrhages also had a large hemorrhage into the rectus muscle sheath.

In two cases petechiae were observed in the skin. In one of these the petechiae were generalized; in the other they were limited to the feet. In two cases there were large ecchymoses in the skin. In one of these the ecchymotic area was located below the left axilla; in the other there was an ecchymosis below the right axilla and another in the scrotum.

DISCUSSION

From this study it appears that the cardiac changes in this series of cases of scrub typhus fever were exceeded in frequency only by pulmonary changes. Cardiac involvement was more frequent than meningoencephalitic lesions. Although cardiac changes occur in the great majority of fatal cases, they are present in varying degrees of severity. And, finally, it is apparent that, in a considerable proportion of patients with carditis, congestive heart failure, hitherto only vaguely and uneconvincingly alluded to in the available clinical literature, actually develops.

The changes described here are quite similar to those found in European (epidemic) typhus fever.¹² The detection of endothelial proliferation in this series confirms the findings of Corbett.⁶ This lesion was obvious in the smaller and medium-sized vessels of the heart, but not in the larger coronary vessels. Similar proliferative changes were sought, but not found, in the adventitial vessels of the gut, in the vasa vasorum of the aorta, and in the afferent arterioles of the renal glomeruli. The endothelial hyperplasia is not unlike that which has been described in European typhus. But here the similarity ends, because neither endothelial necroses nor thromboses were observed in the present series. The incidence of pericardial or endocardial infiltration was rather unusual in this series. In none of Corbett's seven cases⁶ was endocardial infiltration described and in only one was subepicardial infiltration found.

The existence of adrenal changes, previously denied^{13, 14} or not mentioned, is of some interest. These glands obviously are involved to some extent in the general picture of visceral congestion. They also show the same hemorrhages and focal necroses that other organs show. The changes are similar to those found in other infections, such as diphtheria, or in intoxications such as that produced as a result of the injection of diphtheria toxin.¹⁵ Massive adrenal hemorrhage was not seen in the present series, and it is doubtful that any of the fatalities are attributable to acute adrenal insufficiency. Whether or not the asthenia, tachycardia, hypotension, and effort intolerance seen as the most striking sequelae of scrub typhus fever are related to the observed changes in the adrenals seems questionable.

Although it is more than likely that alterations in the walls of the blood vessels are responsible for the bleeding phenomena, references have appeared in the literature^{13, 17} to a "diminished coagulability of the blood" in the disease. The results of investigation of intrinsic changes in the clotting mechanism are awaited with interest.

THE QUESTION OF RESIDUAL CARDIAC DAMAGE

As in Corbett's group, variable degrees of damage to the myocardial fibers were found in the present series. Of twenty-five cases with myocarditis, twelve showed myocardial necrosis of some degree. When present it was heaviest in the neighborhood of focal perivascular exudates or in the subendocardium. Accumulating clinical¹⁶ and anatomic evidence tends to show, however, that

these changes eventually disappear, leaving no trace of previous damage. Williams, Sinclair, and Jackson⁹ found neither cellular infiltration nor evidence of early fibrotic changes in the hearts of three soldiers who died of complications four to six weeks after attacks of scrub typhus. A more recent autopsy¹⁰ performed on a soldier who died on the thirty-fifth day of scrub typhus from a complication not directly related to the disease showed identifiable, but practically completely healed, myocardial lesions. The resulting scar tissue was regarded as so slight as to be unlikely to interfere with normal function. The following case of a patient personally observed is very instructive because of the long period following the attack of scrub typhus fever and the occurrence of cardiac symptoms in the interim.

REPORT OF CASE

CASE 32.—In May, 1944, a 22-year-old infantryman had a severe attack of scrub typhus fever, associated with an eschar, a rash, regional and generalized lymphadenopathy, and a strongly positive OX-K agglutination reaction. The disease ran a two weeks' course with deafness, delirium, cough, cyanosis, signs of pneumonia, tachycardia, and hypotension. He was so sick that his name was placed on the seriously ill list. Following recovery he complained persistently of breathlessness and tachycardia on exertion, palpitation, precordial oppression, weakness, and exhaustion. These symptoms continued until November, 1944, when the patient developed severe acute infectious hepatitis which progressed to fatal acute yellow atrophy of the liver. Post-mortem examination showed a perfectly normal heart without infiltration or scarring.

Similar observations have been made following European typhus,¹² in which the heart is involved as severely and extensively as in scrub typhus, and also following diphtheria in which there is much more severe and extensive myocardial necrosis. There has been no question of chronic heart disease following either of these diseases. From the available evidence it is likely, therefore, that patients who survive scrub typhus fever ultimately show no residual cardiac damage.

SUMMARY AND CONCLUSIONS

1. Post-mortem studies carried out in thirty-one cases of scrub typhus fever showed pulmonary lesions in all but one case and cardiac lesions in twenty-five. Meningoencephalitic lesions were third in order of frequency.

2. The essential pathologic response to the infection consisted of endothelial proliferation and perivascular lymphocytic, plasma cell, and mononuclear cell infiltration.

3. The principal cardiac changes were in the myocardium, but the endocardium and pericardium frequently contained cellular exudates. These were lesions occurring in patients who succumbed to the disease during the acute phase and their presence lends no support to the hypothesis that myocardial damage persists in patients who have recovered from the disease. Necrosis of heart muscle fibers was observed in about half of the cases showing carditis. This was rarely severe.

4. The pathologic changes in various organs represent the composite effect of at least three possible factors: (a) The disturbance of blood supply pro-

duced by vascular injury and occasionally manifested by focal necrosis and hemorrhage, (b) the back-pressure effects from congestive heart failure, and (c) inflammatory changes.

5. Hemorrhagic phenomena were frequently observed. They were probably due to vascular injury. Petechial hemorrhages or ecchymoses occasionally were found in the skin.

6. Evidence does not point to residual cardiac damage in scrub typhus.

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THE PERIPHERAL BLOOD FLOW UNDER BASAL CONDITIONS IN OLDER MALE SUBJECTS WITH NORMAL AND ELEVATED BLOOD PRESSURES

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IN RECENT years, the peripheral circulation has been the subject of new interest because of the added attention which has been given to inflammatory, occlusive, and vasospastic states of the peripheral vessels. We have been interested in that part of the volume output of blood from the heart which is allotted to the peripheral circulation. In studies of normal male subjects in the earlier decades we found that 73 c.e. per square meter of body surface per minute was the average amount of blood allotted to the peripheral circulation in a room at 27° C. with a humidity of 50 per cent.¹ However, this was reduced to 52 c.e. per square meter of body surface per minute when the room temperature was 25° C. The differences which are encountered in the peripheral blood flow of subjects in the later decades who had clear-cut evidences of vascular disease form the basis of this report. The clinical diagnoses shown in Table I indicate that these patients exhibited a wide range of generalized vascular disease, such as arteriosclerotic heart disease, hypertension, coronary artery disease, angina pectoris, coronary thrombosis, and generalized arteriosclerosis.

The peripheral blood flow has been measured on 27 occasions in 25 male subjects from 38 to 77 years of age. The blood pressure was in the normal range in 12 subjects and was elevated in 13 subjects; these groups are designated as the "normal blood pressure group" and the "hypertensive group," respectively.

METHODS

Measurements of peripheral blood flow were made by modifying the method of Hardy and Soderstrom² in such a way that the use of a calorimeter was not necessary. This modification has been described previously.³⁻⁵ The following data are required: skin temperatures at eleven points on the anterior surface of the body, as shown in Fig. 1³; rectal temperature; oxygen consumption; height; and body weight. In this method is measured the amount of blood allotted to the periphery of the whole body to a depth of 1 cm. below the surface. Blood pressure and pulse rate are recorded.

The skin temperatures were measured with the Hardy-Soderstrom radiometer⁶; the rectal temperature was measured with a single-junction, copper-constantan thermocouple⁶; and the oxygen consumption was measured with a

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TABLE I. DATA RELATING TO TWENTY-FIVE MALE PATIENTS FROM 38 TO 77 YEARS OF AGE, EXHIBITING VASCULAR DISEASE, AT ROOM TEMPERATURE OF 27° C.

CASE AGE (YRS.) HISTORY NO.	PERIPH- ERAL BLOOD FLOW (C.G./M. ² /MIN.)	AVER- AGE RECTAL TEMPER- ATURE °C.	AVER- AGE WEIGHT- ED SKIN TEMPER- ATURE °C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS
				Normal Blood Pressure Group														
				1 °C.	2 °C.	3 °C.	4 °C.	5 °C.	6 °C.	7 °C.	8 °C.	9 °C.	10 °C.	11 °C.				
N. H. 53	53	37.58	34.16	35.3	34.9	34.4	34.2	34.4	34.7	35.2	33.8	32.9	33.3	33.6	107/65	75	- 8	Arteriosclerotic heart dis- ease. Angina pectoris.
D. G. 63	81	36.89	34.19	35.1	34.7	34.3	34.6	33.9	33.7	34.4	34.3	33.2	33.7	34.3	115/75	65	- 9	Anemia Arteriosclerotic heart dis- ease. Coronary thrombo- sis
J. S. 52	39	36.91	34.12	35.0	34.7	34.3	34.7	34.4	34.7	35.0	33.7	33.6	32.7	33.5	149/75	55	- 1	Arteriosclerotic heart dis- ease. Enlarged heart
M. K. 67	114	36.94	33.44	34.7	34.7	33.7	33.8	33.8	33.8	33.3	33.3	32.4	32.1	32.0	120/79	63	+30	Arteriosclerotic heart dis- ease. Coronary artery disease. Enlarged heart
N. M. 38	166	37.18	34.45	35.7	35.3	35.1	35.4	34.5	34.6	35.3	34.3	33.8	32.7	32.4	108/68	70	+37	History of fluctuation in blood pressure and of be- ing high in last two years
F. S. 54	56	37.32	34.54	35.5	35.5	35.3	35.2	34.9	34.3	34.9	34.5	32.4	33.6	34.0	148/90	72	- 5	Hypertensive heart disease. Angina pectoris. Auricu- lar fibrillation
H. S. 70	84	36.40	33.48	34.6	34.0	33.4	33.4	33.2	32.9	34.5	32.4	33.3	32.9	33.8	107/64	62	-0.4	Arteriosclerotic heart dis- ease. Coronary artery dis- ease. Angina pectoris. Enlarged heart
A. K. 81	62	36.70	33.79	34.4	34.3	33.9	34.2	33.4	33.3	34.8	34.0	32.8	32.9	33.8	127/61	56	+ 4	Arteriosclerotic heart dis- ease. Coronary thrombo- sis. Generalized arterio- sclerosis
C. T. 52	47	37.20	34.60	35.2	35.0	34.8	35.2	34.7	34.0	34.7	34.6	34.5	33.8	33.9	115/64	60	- 4	Arteriosclerotic heart dis- ease. Enlarged heart. Au- ricular fibrillation. Pul- monary fibrosis
L. M. 65	46	37.13	33.60	34.7	34.8	33.4	34.9	35.6	33.2	35.0	32.4	34.1	31.6	32.1	132/70	71	+36	Arteriosclerotic gangrene of the right foot. Observa- tion 41 days after ampu- tation

[illegible]

TABLE I.—CONT'D

CASE AGE (YRS.) HISTORY NO.	PERIPH- ERAL BLOOD FLOW (C.C./M. ² /MIN.)	AVER- AGE RECTAL TEMPER- ATURE °C.	AVER- AGE WEIGHT- ED SKIN TEMPER- ATURE °C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS
				1 °C.	2 °C.	3 °C.	4 °C.	5 °C.	6 °C.	7 °C.	8 °C.	9 °C.	10 °C.	11 °C.				
Hypertension Group—Cont'd																		
S. McD. 48	25	37.11	33.52	34.9	34.5	33.7	33.5	33.9	33.6	34.2	33.1	32.2	33.0	32.5	177/133	68	-11	Hypertensive cardiovascular heart disease
93209																		
W. C. 48	62	37.27	34.30	35.3	35.1	34.5	34.7	34.4	34.2	35.0	33.7	33.5	33.2	34.4	198/113	66	-1	Hypertensive cardiovascular heart disease. Myocardial infarction. Arteriosclero- sis. Coronary thrombosis.
373325	70	37.10	33.97	35.0	34.8	34.3	34.3	33.8	34.2	34.8	32.9	33.2	32.9	34.5	193/112	66	0	Hypertensive heart disease. Coronary thrombosis. Coronary thrombosis
J. S. 44	21	37.46	33.86	35.0	34.4	34.2	34.4	34.0	33.9	34.8	33.5	32.6	32.6	33.4	211/126	62	+4	Chronic pyelonephritis. Hy- pertensive heart disease. Coronary artery disease.
353263																		
P. L. 53	79	37.40	33.71	34.0	34.8	33.8	34.6	33.7	33.0	34.5	33.2	33.1	32.3	34.1	197/103	83	+20	Hypertension. Arterioscler- otic heart disease. Auricu- lar fibrillation
384879	87	37.30	33.80	35.1	35.4	34.8	34.9	34.3	34.4	34.2	33.1	33.0	31.8	31.4	176/87	72	+36	Hypertension. Arterioscler- otic heart disease
H. S. 77																		
109660	91	37.01	34.35	35.0	35.0	34.9	35.4	34.5	34.0	34.4	34.8	33.5	33.2	32.8	163/91	74	+23	Hypertension. Arterioscler- otic heart disease
377456																		
Average	55	37.32	33.92	35.0	34.8	34.5	34.6	34.2	34.0	34.4	33.5	32.8	32.5	32.6	194/117	77	+9	
Standard devi- ations about the means	24	0.26	0.35	0.4	0.5	0.5	0.6	0.4	0.4	1.0	1.4	0.6	0.6	1.4	22/19	10	14	
Average from both groups	63	37.18	33.93	34.9	34.8	34.4	34.5	34.2	33.9	34.6	33.5	33.0	32.6	32.9	156/98	72	+9	
Standard devi- ations both groups about the means	31	0.39	0.38	0.5	0.5	0.6	0.6	0.4	0.5	0.8	1.2	0.7	0.7	1.3	41/27	11	15	
Normal Subjects in Third Decade*																		
Average	73	36.79	33.74	34.4	34.2	34.1	34.2	33.8	33.7	34.4	33.2	33.2	33.2	32.7	105/71	61	-5	
Standard devi- ations about the means	30	0.16	0.33	0.3	0.4	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.5	1.9	5/5	7	10	

*Stewart and Evans.¹

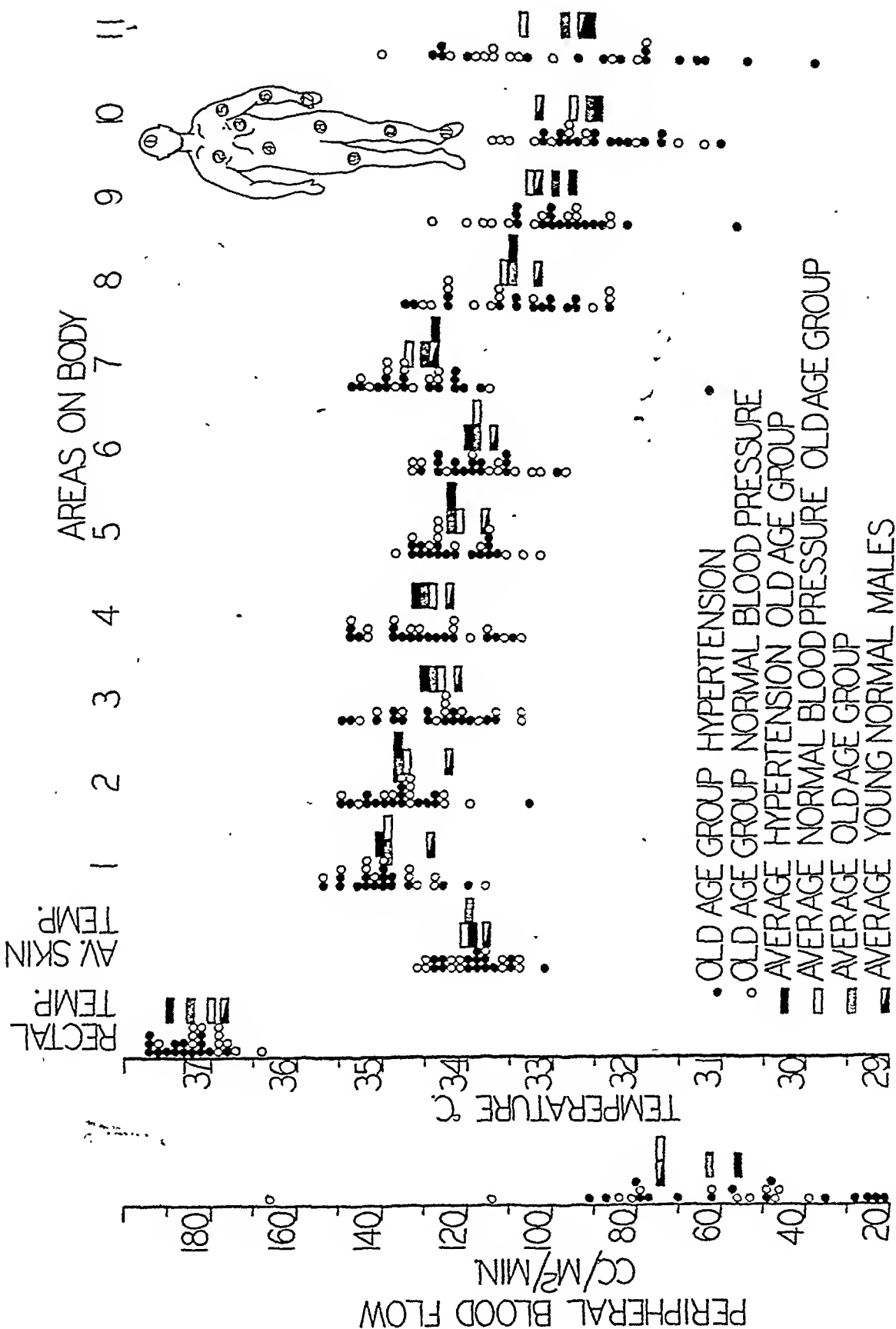


Fig. 1.—In this figure are shown the peripheral blood flow, rectal temperature, average weighted skin temperature, and temperature of 11 areas on the anterior surface of the body in 25 patients from 38 to 77 years of age. Open circles represent those with normal blood pressure, and closed circles represent those with hypertension. The averages for all patients in each category are shown by appropriate symbols. The averages for normal young male subjects are shown for comparison.

Benedict-Roth metabolism apparatus.⁷ The basal metabolic rate was calculated from the Mayo Foundation standards for age and sex,⁸ and the surface area was calculated from the tables of DuBois and DuBois.⁹

PROCEDURE

All observations were made in the morning, when the patients were in a basal metabolic state. The rectal thermometer was inserted to a depth of 10 cm. as soon as the patient reached the constant temperature room and remained in place during the morning's observations. The subjects lay nude in bed, covered only with a sheet. The room temperature was maintained at or near 27° C., and the humidity ranged between 45 and 50 per cent. In order to become accommodated to this environment, the patients lay at rest for one hour before observations were started. Three to eight sets of observations were made, from which it was possible to make two to seven calculations of peripheral blood flow. In some instances the oxygen consumption was measured at the end as well as at the beginning of the observations. In some instances ten-minute and, in others, twenty-minute intervals were chosen for making the measurements of skin temperatures, and the formulas used in making the calculations were adjusted accordingly.⁵

OBSERVATIONS

The results of the observations are shown in Table I and Fig. 1.

Peripheral Blood Flow.—The data are recorded in Table I, and the scatter diagram of the peripheral blood flow calculations is shown in Fig. 1. On the whole, the peripheral blood flow in the group with normal blood pressure was greater than in the group with elevated blood pressure, although there was some overlapping. The average peripheral blood flow for the normal blood pressure group was 73 e.e. per square meter of body surface per minute, the same as that found in normal young individuals at this temperature.¹ In the group with hypertension, however, it was only 55 e.e. per square meter of body surface per minute, or approximately the same as that found in normal subjects at the lower room temperature of 25° C. The average for the combined groups was 63 e.e. per square meter of body surface per minute.

Rectal Temperature.—The average rectal temperature for the group with normal blood pressure was 36.95° C.; for the group with hypertension, 37.32° C.; and for the combined groups, 37.18° C. (Table I, Fig. 1). Therefore, the rectal temperature of the group with hypertension was 0.37° C. higher, on an average, than that of the group with normal blood pressure, and in both groups the rectal temperature was higher than it was in normal young men, in whom it averaged 36.79° C.

Weighted Skin Temperature.—The weighted skin temperature averaged 33.99° C. for the group with normal blood pressure and 33.92° C. for the group with hypertension; it was 33.93° C. for the groups combined, as compared with 33.40° C. for the group of normal young men (Table I, Fig. 1). In short the average skin temperature was higher in this older age group with vascular disease than in the younger normal subjects.

Temperatures of the Hands.—The average of the temperatures of the hands (Area 7) was 34.7° C. for the group of older subjects with normal blood pressure and 34.4° C. for the group with hypertension. That is to say that the average hand temperatures in the older group with normal blood pressure are slightly higher than those in the group of normal young men, whose hand temperatures averaged 34.4° C. In the group with hypertension the average hand temperature of 34.4° C. was the same as that in the normal group.

Temperatures of the Feet.—The average of the temperatures of the feet was 33.4° C. for the group of older subjects with normal blood pressure and 32.6° C. for the hypertension group (Table I, Fig. 1). The feet were therefore warmer in the group with normal blood pressure than in the group of normal young men in which the temperatures of the feet averaged 32.7° C.; in the hypertension group the temperatures of the feet were slightly below normal.

Temperatures of Other Areas of the Body.—For Areas 1 to 6, inclusive, of the body surface, that is, for the upper part of the body, the skin temperature was higher in the hypertension group than in the group with normal blood pressure, each being appreciably higher than in normal young subjects (Table I, Fig. 1). Beginning with the hands (Area 7), however, and continuing to the lower part of the body and the feet (Areas 7 to 11, inclusive), the relationship of the first two groups is reversed: in these areas the temperatures in the group with hypertension are cooler than in the normal blood pressure group. As compared with normal young subjects, the group of older subjects with normal blood pressure, except for the shin (Area 10), show higher temperatures. On the other hand, in the hypertension group the temperatures are lower than normal except in the hands (Area 7), where it is the same, and in the upper thigh (Area 8) where it is higher. The averages for the normal blood pressure group and hypertension group are higher than the averages for the normal young group for all areas except 9 and 10, namely the lower thigh and shin.

Blood Pressure.—The average of the blood pressure for the older subjects with normal blood pressure was 124/73, and 194/117 for the hypertension group, the average for the two combined groups being 156/98, as compared with 105/71 for the group of normal young men (Table I, Fig. 1).

Heart Rate.—The average heart rate for the older group with normal blood pressure was 65 per minute; for the hypertension group slightly higher, 77 per minute; and for both groups 72 per minute (Table I, Fig. 1). These are to be compared with the rate of 61 per minute in the group of normal young men.

Basal Metabolic Rate.—The basal metabolic rate was essentially the same for the normal blood pressure and hypertension group, namely +7 per cent and +9 per cent, respectively, as compared with -5 per cent for the group of normal young men (Table I, Fig. 1).

DISCUSSION

It appears, therefore, from observations made on these patients that there are certain differences in the peripheral circulation in older men as compared with normal young men. This is the case not only in those older men with

normal blood pressure but also in those with hypertension. In only one of the patients (L. M., No. 255998, Table I) in this study were there signs or symptoms of occlusive peripheral vascular disease. In the normal young subjects already reported¹ it was found that more blood was allotted to the periphery when the environmental temperature was 27° C., than at a lower temperature of 25° C.

The data relating to this older age group have been subjected to statistical analysis. On comparison of the hypertension group with the normal blood pressure group none of the differences were significant when the test of twice the standard deviation was applied; but there was a trend toward decrease in peripheral blood flow, increase in rectal temperature, and decrease in average weighted skin temperature, with increase in temperature of the upper parts of the body and decrease in temperature of the lower parts of the body.

When the older people with normal blood pressure are compared with young normal individuals, again the differences are not statistically significant. The peripheral blood flows are the same. The trend is for the rectal and average weighted skin temperature and the temperature of all the areas of the body to be increased in older people.

Again in older people with hypertension as compared with young normal subjects the differences are not significant, but there is a trend toward decrease in peripheral blood flow, an increase in rectal (all over 37° C. except one subject) and in average weighted skin temperature, and an increase in temperature of the upper part of the body and a decrease in the lower part.

When the whole old age group, including those with hypertension as well as those with a normal blood pressure, are compared with normal subjects, no statistically significant differences are revealed; but again the trend is toward a decrease in peripheral blood flow, a rise in the rectal and the average weighted skin temperatures, and a rise in temperature of the upper part of the body and a decrease in the lower part.

How can these data be fitted together? There is a trend toward decrease in peripheral blood flow when there is hypertension, with a rise in rectal and a decrease in average weighted skin temperature, both as compared to normal young subjects and to older subjects with normal blood pressure. Also it would appear to be more than chance that the temperature of the upper part of the body is warmer and that of the lower part is cooler in these hypertensive subjects than in those subjects in the same age group with normal blood pressure, a pattern which is similar to that exhibited by hypertensive patients in the earlier age group.¹⁰

SUMMARY

The peripheral blood flow and skin and rectal temperatures have been measured in 25 male patients from 38 to 77 years of age, that is to say in patients in the older age group. In 12 subjects there were clinical signs of vascular damage without hypertension, and in 13 there was also hypertension. In only one subject was there evidence of occlusive peripheral vascular disease. The results in these patients have been compared with those in normal young male

subjects. The peripheral blood flow was measured by a modification of the method of Hardy and Soderstrom. The following facts emerged:

1. The average peripheral blood flow at 27° C. (room temperature) is in the same range in older individuals with normal blood pressure, 73 c.c. per square meter of body surface per minute, as in younger male subjects, but is lower, namely 55 c.c. per square meter of body surface per minute in those with hypertension, and approaches the value recorded for normal young subjects at the cooler environmental temperature of 25° C.

2. The rectal temperature is higher in older people than in the young normal group (36.79° C.) and was slightly higher in the hypertension group (37.32° C.) than in the normal blood pressure group (36.95° C.).

3. The average weighted skin temperature was higher in both the normal blood pressure group (33.99° C.) and the hypertension group (33.92° C.) than in younger subjects (33.74° C.).

4. The skin temperatures of the individual areas of the body surface are warmer in the older patients with normal blood pressure than in younger individuals, except in one area, namely the shins (Area 10), where the temperature is lower in the older group. On the other hand patients with hypertension in the older age group have a warmer skin temperature in the upper part of the body, and a cooler temperature in the lower part of the body than do young normal subjects. The inference is that the peripheral blood flow to the feet is reduced, since their temperature is lower, and that the blood flow to the upper part of the body is increased, since its temperature is warmer. The reduction in peripheral blood flow in the lower part of the body is apparently greater than the increase in the upper part of the body so that the net result is an average peripheral blood flow for the whole body which is less than the value in normal young males at the same room temperature. In short, it is comparable to the constriction observed in normal young subjects in an environment of 25° C.

5. Patients with hypertension in this older age group show the same trends, but to a lesser extent, as are shown by patients with hypertension in the earlier decades.

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INTERATRIAL AND SINOATRIAL BLOCK, WITH AN ILLUSTRATIVE CASE

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ALTHOUGH atrioventricular conduction disturbances are common and have been widely studied, the subject needs further investigation. Block between the two atria is rare, and little attention has been paid to it either experimentally or clinically. That it may occur has been recognized for many years, and a few undoubted clinical examples have been recorded.

If the pacemaker of the heart resides in the S-A node, the excitation wave should first pass to the adjacent right atrium before reaching the left, whether the wave spreads like "fluid poured upon a flat surface,"¹ or through functionally differentiated pathways in the muscle bands. The existence of an interval between contraction of the two atria was first recognized by Chauveau² in the horse, and later by Hering³ in the dying hearts of smaller laboratory animals. This observation was confirmed by Frederieq,⁴ Schmidt-Nielsen,⁵ and Stassen.⁶ This interval was measured electrically by Garten,⁷ who set it at 0.0128 to 0.0139 second, apparently on the basis of experimental work done by Erfmann⁸ and by Schneiders.⁹ In 1916 Baehmann,¹⁰ using a mechanical method, obtained a similar average, 0.013 second.

Dissoeiation between the two atria, either partial or complete, was first recorded in 1900 by Hering,³ who also first emphasized that poor nutrition of the myocardium of the dying heart predisposed to block. Frederieq⁴ divided the two atria of hearts perfused by the Langendorff method and noted the development of independent rhythms in the two parts. Later studies^{11, 12} on hearts *in situ* supported these earlier experiments. Similar results were obtained by Baehmann,¹⁰ Condorelli,¹³ and Scherf and Siedek.¹⁴

Although Keith and Flack¹⁵ and Thorel¹⁶ thought that there were differentiated anatomic connections between the S-A node and the A-V node, their view has never been substantiated. The presence of functionally specialized conducting pathways within the atrial muscle bands was first postulated by Eyster and Meek,¹⁷ who believed that they had demonstrated the existence of a special path from the S-A to the A-V node; later they¹⁸ offered additional evidence in support of this theory in order to refute the criticism of Lewis and his associates.¹⁹ Rothberger and Scherf²⁰ found that by tying one or both of two muscle bands, the first passing from the upper part of the S-A node to the left atrium, the second from the lower part of the S-A node along the Torus Lowerii through

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the interatrial septum to the A-V node, it was possible to interrupt the conduction of the sinus impulse to the ventricle and so to produce A-V nodal rhythm. When both pathways were broken, they assumed that the spread of the sinus impulse was through numerous secondary pathways to the atria and A-V node. Condorelli²¹ listed eight separate connections between the S-A and A-V nodes, the most direct of which were the two tied by Rothberger and Scherf and a third originating in the middle of the S-A node and running into the interatrial septum. He stated that all fibers going to the A-V node united at one place in the lower part of the interatrial septum, between the coronary sinus and the fossa ovalis. If these pathways actually exist, one important implication of their presence would be the possibility suggested by Condorelli,²¹ that their integrity, associated with impairment of fibers from the S-A node to the atrial muscle, might lead to shortening of the A-V conduction time as measured by the P-R interval.

Experimental evidence for the existence of a special pathway between the two atria was adduced by Erfmann.⁸ Better known is the work of Bachmann,¹⁰ who described the interatrial bundle (Bachmann's bundle) as follows: "In a dog's heart of average size the right extremity of the band originates about 5 mm. to the mesial side of the auriculo-oval angle and in a direct line with it. This extremity of the band is immediately back of the aorta and spreads in a fan-like manner onto the mesial (right) auricular wall and the root of the superior vena cava. From this origin the band sweeps in an almost straight line to the base of the left auricular appendage but, so far as superficial appearance indicates, its fibers can be traced to near the tip of the left appendage. The band is thinnest near its origin on the right side where it has an angular appearance. It then broadens gradually as it passes to the left auricle. The band is slightly concave from right to left, the concavity being directed upward. It has a length of about 20 mm." Clamping this muscle band led to a prolongation of the interval between contraction of the two atria from a normal average of 0.013 second to an average of 0.05 second; in one instance the interval was as great as 0.98 second. Rothberger and Scherf²⁰ found that clamping this region produced various changes in the form of the P waves and an increase in the interatrial interval. They also observed a small artery which supplied this area. The origin and course of this artery was more carefully ascertained by Condorelli,¹³ who succeeded in tying it in the experimental animal.

In the human heart, Spalteholz²² designated this vessel as the *ramus atrialis sinister anterior*. Condorelli found that in the dog heart it might arise from the main left coronary artery or from the initial segments of either the anterior descending or circumflex branches. The latter origin was more common. Diagrams in Condorelli's paper show the artery clearly; it is also shown in Schlesinger's diagram, reproduced from Spalteholz. In several instances Schlesinger's²³ x-ray photographs show the vessel and it may also be identified in Gross' illustrations.²⁴ One illustration in a textbook of anatomy²⁵ shows the origin of this vessel. Shortly after its origin the artery sends an auricular branch to the left auricular appendage. The vessel then passes up and to the right, along the path of Bachmann's bundle, terminating in small twigs to the wall of the su-

perior vena cava near the sinoatrial node. This latter region is also supplied by the ramus atrialis dexter anterior, which arises from the first part of the right coronary artery.

Condorelli¹³ found that ligation of the left anterior atrial artery produced changes in the P wave and in the sequence of atrial contraction which were similar to those produced by clamping or tying Bachmann's bundle. In two instances fibrillation was present in the left atrium, while a sinus rhythm, conducted to the ventricles, persisted in the right atrium. Analogous dissociation was produced by tying the anterior descending coronary artery near its origin from the left coronary artery, and in one animal interatrial block was produced, beginning with two-to-one and later progressing to complete block, in which sinus rhythm was seen in the right atrium, while there was complete standstill of the left atrium. Similar results were obtained by Scherf and Siedek¹⁴ in poorly perfused Langendorff hearts and in hearts in situ whose interatrial artery had been tied. Condorelli and Scherf and Siedek emphasize the importance of an intact blood supply in maintaining normal relationships in the contraction of the two atria.

Clinical examples of interatrial dissociation are relatively few. The first case was recorded by Schrumpf,²⁶ whose patient was a 37-year-old man with rheumatic mitral stenosis and aortic insufficiency. During an episode of acute heart failure, he was given digitalis in toxic amounts. Electrocardiograms taken at this time showed two sets of P waves: P_1 with a rate of 64 per minute which was conducted to the ventricles with a P-R interval of 0.20 second, and P_2 with an independent rhythm and a rate of 109 per minute, which was not conducted to the ventricles. P_2 disappeared after three days, possibly because the digitalis was withdrawn. Schrumpf's assumption that these two independent series of P waves were due to two active S-A nodes has not been generally accepted.

Scherf and Siedek¹⁴ have reported another case of partial interatrial block in a patient with an acute coronary thrombosis, which at necropsy was found to be in the left coronary artery just before its bifurcation into the circumflex and anterior descending branches. Complete A-V block was present, and the interatrial conduction time varied between 0.24 and 0.40 second. Although Scherf and Siedek made no mention of the interatrial artery, its usual origin is just distal to the occluded area, and presumably the supply of blood to the interatrial band was deficient.

Three more cases were reported by Bay and Adams.²⁷ Electrocardiograms of the first patient, a 22-year-old man with acute rheumatic fever, showed two independent sets of P waves: P_1 with a rate of 85 per minute, conducted normally to the ventricles; and P_2 with an average rate of 113 per minute. The second patient was a 9-year-old girl, and the third a 25-year-old man with chronic glomerulonephritis; electrocardiograms of both patients showed extra sets of complexes which may be atrial in origin, but whose appearance suggests strongly that they may be artifacts. Bay and Adams accepted Schrumpf's explanation for such findings and discussed extensively the possibility of anatomic and functional separation of the S-A node into two parts.

In 1935, Géraudel²⁸ recorded two instances of independent atrial rhythms in elderly patients with Cheyne-Stokes respiration. The P waves which were not conducted to the ventricles were more numerous during the polypneic phase of respiration. Duclos²⁹ reported one example of independent atrial rhythms in a 9-year-old girl who had no cardiovascular symptoms or other abnormal findings. Electrocardiograms showed two independent sets of P waves, one of which was regularly conducted to the ventricles. Tracings made on two subsequent occasions did not show these abnormalities. Dominguez and Bizzozero³⁰ found an example of double atrial rhythm in a 6-day-old infant; the P waves which were conducted to the ventricles occurred at a rate of 136 per minute; the independent P waves, of different contour and seen in both Lead I and III, had a rate of 110 per minute. They found only this single case among two hundred newborn infants examined electrocardiographically, although they quote Burghard and Wunnerlich³¹ as having observed the so-called "double commande" in ten of thirty-two infants.

Lian and Golblin³² have recorded a similar case. The patient, who was 71 years old, had had a coronary artery occlusion five years before. The second examination was done because of convulsive seizures. The electrocardiogram showed two-to-one A-V block, with bundle branch block, as well as deep Q waves in Leads II and III. Using the special lead designed to give large atrial complexes, from the manubrium to the fifth right intercostal space at the sternal border, Lian and Golblin recorded two series of P waves. One series, with a rate of 88 per minute, showed the two-to-one block; the other series, consisting of deeply negative waves, had a rate of 76 per minute and was independent of the first series. The authors point out that their curves, which were obtained from a patient with coronary artery occlusion, resemble those recorded by Scherf and Siedek in experimental interatrial block which was produced by clamping the small artery supplying the Bachmann bundle.

Hertz³³ also reported one case; the patient was a 17-year-old girl who had had a large goiter removed a year before because of tracheal compression. The electrocardiograms showed two sets of P waves, each occurring at about the same rate of 55 per minute, with one set conducted to the ventricles with a P-R interval of 0.15 second. It is not certain that the two sets are independent; there appears rather to have been a transient delay in interatrial conduction, with rapid return to normal.

Luisada³⁴ has reviewed the subject of both partial and complete interatrial dissociation, with particular reference to the work of his Italian colleagues. His own electrocardiograms were simultaneous records of an esophageal lead, for the left atrium, and a mouth-xiphoid lead, for the right atrium. He demonstrated delay in left atrial response, particularly in mitral stenosis, and showed several curves which he interpreted as representing flutter in the right atrium with fibrillation in the left. Delay in left atrial response in mitral stenosis was also described by Mahaim.³⁵ The widely notched P waves that he described are exaggerated examples of the notched P waves commonly seen where there is enlargement of the left atrium in mitral stenosis.

Several cases are on record which have been interpreted as dissociation of the atria, with longitudinal dissociation of the ventricles as well (Hoffmann,³⁶ Burghard and Wunnerlich,³¹ Kerr and Sampson,³⁷ and Géraudel^{38, 39}). Other cases have been thought to represent interatrial dissociation, but have subsequently received a different interpretation. The first such case was that of Wenckebach,⁴⁰ who also was the first to propose a clinical diagnosis of interatrial dissociation. Other similar cases have been reported by Roth,⁴¹ Danielopolu and Proca,⁴² Kure and Kaneko,⁴³ and Lombardini and Aviles.⁴⁴

REPORT OF CASE

Our patient was a 36-year-old Negro woman, who entered the John Sealy Hospital on Oct. 9, 1944, because of severe nausea and vomiting of three weeks' duration. She had had severe headaches during the preceding three years, and blurring of vision had been marked for three days before admission. Her blood pressure was 222/170; the fundi showed marked hypertensive retinopathy, with papilledema. On October 10, the blood nonprotein nitrogen was 57 mg. per 100 c.c.; the creatinine 5.1 mg. per cent. These values rose gradually, and, on November 10, the nonprotein nitrogen was 259 mg. per cent. Venous pressure and circulation time were normal. The gastrointestinal symptoms persisted, and in addition the patient suffered several attacks of severe epigastric and substernal pain. She became stuporous; muscular twitching occurred repeatedly; and on November 4 she had a generalized convulsion. On November 13 the heart was first noted to be irregular, with apparent dropping of every third beat. The patient died on Nov. 15, 1944.

The electrocardiograms taken on October 10 showed changes consistent with hypertensive heart disease (Fig. 1). Surprisingly favorable changes took place during the next few weeks, so that, on November 7, the T waves in Leads I and II, which were previously negative, had become positive. On November 13 the bigeminy observed clinically was thought to be due to atrial premature beats. The T waves in Leads I and II were high, the S-T segments were slightly elevated and the T waves in Lead CF₂ had become negative. These changes were associated with clinical evidences of uremic pericarditis.

The curve taken on November 14 is reproduced more extensively (Fig. 2), particularly Lead CF₂, since in this curve the atrial complexes are best seen. Preceding the first of each pair of ventricular complexes may be seen two atrial deflections; the first is chiefly positive and is followed, after an interval of 0.28 second by the second deflection, which, though diphasic, is chiefly negative. The second beat of the pair of ventricular complexes is preceded by the same atrial deflections, which, however, are much closer together. In every instance the QRS complex follows the second negative atrial deflection after a uniform P-R interval of 0.18 second.

At necropsy there were 600 c.c. of fluid in the right pleural space and 850 c.c. in the left. The abdominal cavity contained 1,200 c.c. of clear straw-colored transudate. The pericardial sac contained 55 c.c. of opalescent fluid, and there was a thin fibrinous exudate on the pericardial surface. The heart weighed 650 grams; there was moderate atherosclerosis in the coronary arteries, but no occlusion. Early lobular pneumonia was present in the lungs, with edema and chronic passive congestion. There were ulcers in the esophagus, stomach, intestine, and colon. The right kidney weighed 200 grams, the left, 85 grams. The stripped surfaces were finely granular.

The pathologic diagnosis included arteriolar nephrosclerosis, cardiac hypertrophy, fibrinous pericarditis, ulceration of the gastrointestinal tract, pulmonary edema and early lobular pneumonia, hydrothorax, acute edema of the brain, pyelitis, and fibromyomas of the uterus.

Careful dissection of the coronary arteries showed a branch arising a few millimeters from the origin of the left circumflex artery and supplying the left auricular appendage and the area of Bachmann's bundle. This small vessel could be traced across the atria to the region of the S-A node and the wall of the superior vena cava. Its course was perfectly

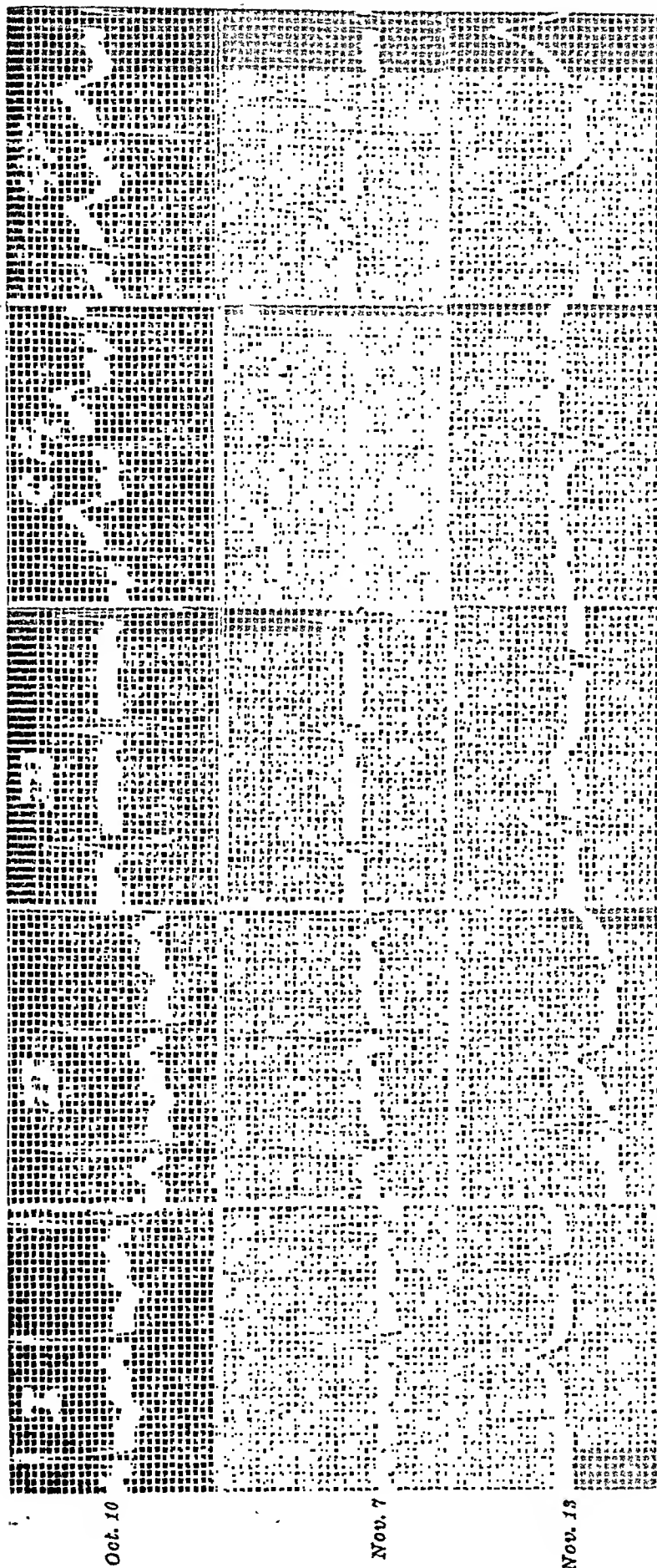


Fig. 1.—Leads I, II, III, CF, and IVF made on Oct. 10, Nov. 7, and Nov. 13, 1944. Note especially Lead CF, on the last date.

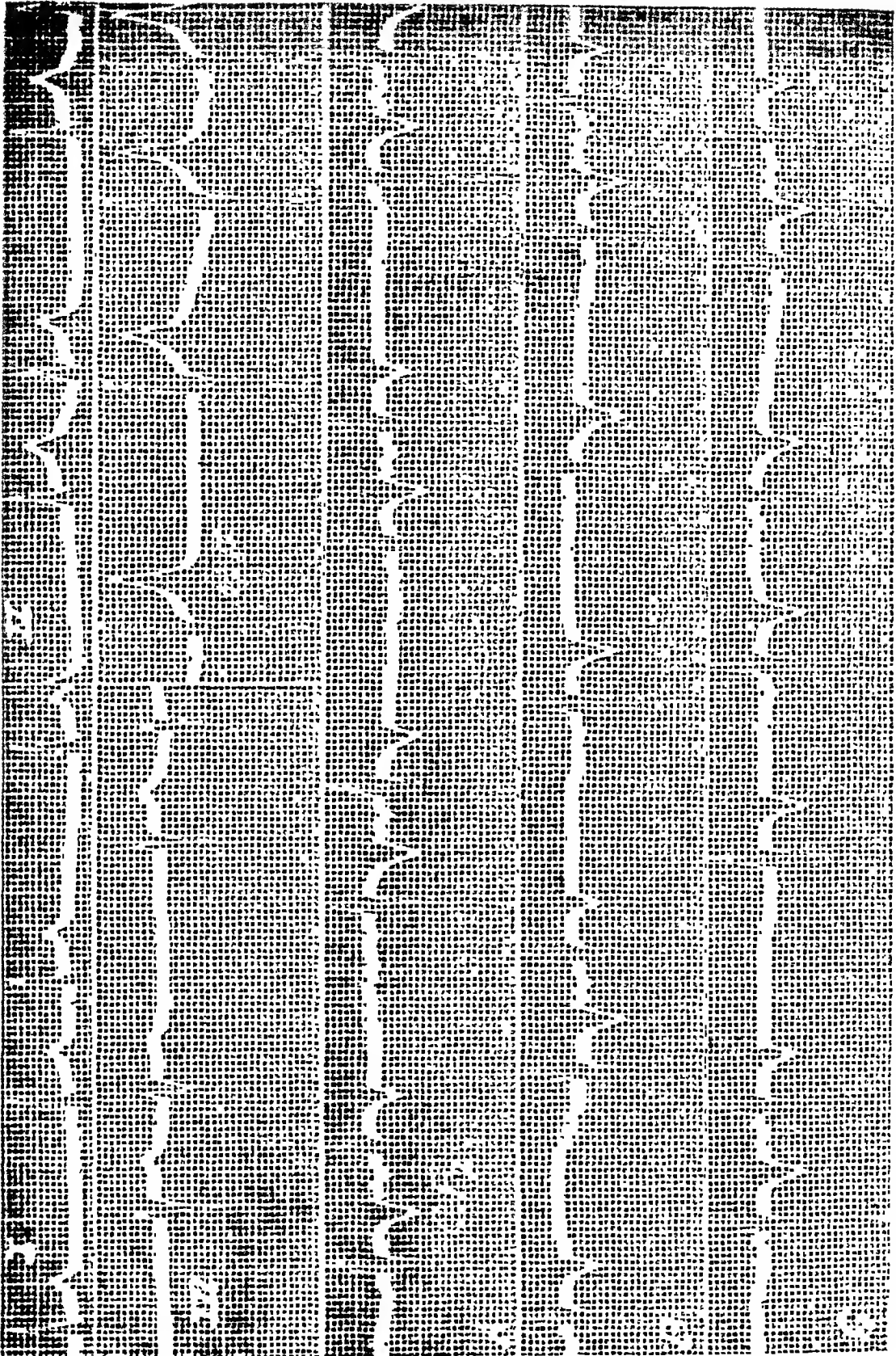


Fig. 2.—The three limb leads and Lead IVF on Nov. 14, 1944, are shown in the first two lines. The last three lines, A, V, and C, are all Lead CFs; B and C are continuous strips. See text and Fig. 3 for comment.

analogous to that of the vessel described in the dog heart by Condorelli.²¹ Multiple sections taken along the course of this vessel showed no evidence of obstruction. The only histologic abnormalities were those due to a moderate uremic pericarditis; the muscle fibers were hypertrophied but otherwise normal.

The large branch of the right coronary artery which supplies the region of the S-A node was likewise carefully dissected and examined. Grossly there was no obstruction, and sections of this vessel showed only a slight intimal fibrosis at one point which decreased the size of the lumen only slightly.

COMMENT

The electrocardiograms of this patient show partial block between the two atria, with loss of normal synchronous excitation. In the absence of any demonstrable anatomic disruption of intra- and interatrial communications, this asynergy must be presumed to be on a functional basis.

The two complexes of atrial origin cannot with certainty be identified with right or left atrial activity. Since the second complex is constantly related to the QRS complex, it is most likely due to right atrial excitation; if this is true, the first atrial complex must, then, be due to left atrial excitation. The converse interpretation is not impossible, since ventricular response to left rather than to right atrial activity was demonstrated experimentally by Seherf and Siedek.¹⁴ This point cannot be determined from the electrocardiogram alone. A simultaneous jugular pulse tracing would have enabled us to identify the response of the right atrium, but unfortunately the patient died before we realized the desirability of such a record.

The wide separation of the two atrial complexes which precede the first of each pair of ventricular beats suggests a partial interatrial block. The atrial complexes which precede each second ventricular beat adjoin each other closely, though each portion can be identified. The same phenomena were present in the electrocardiogram of November 13 (Fig. 1, Lead CF₂), but they were so inconspicuous that they were overlooked at that time, and the bigeminy was interpreted to be due to atrial premature beats. The closer approximation of the atrial complexes preceding the second of each pair of ventricular complexes may be evidence of facilitation of conduction between the two atria, although the explanation which follows seems more logical.

Partial A-V block with dropped beats may be of two kinds: Type I, the Wenckebach type, in which the P-R interval gradually increases until an atrial complex is blocked; or Type II, the Mobitz type, in which the P-R interval is uniform until sudden blocking of an atrial complex takes place. Type I is commonly caused by the action of digitalis, while Type II is more likely to be the result of disease of the conduction pathways. The same concepts may be extended to S-A block.

The common variety of S-A nodal arrest or block needs little comment, since it has been adequately discussed.⁴⁵ The occurrence of the Wenckebach phenomenon, with progressively greater delay in conduction between the S-A node and the atrial tissues, has rarely been commented upon, though it has long been known to exist. In 1908, Rühl⁴⁶ described such a physiologic mechanism quite clearly, basing his reasoning on polygraphic records. Lewis¹ showed diagram-

matically an instance of S-A block in which the impulses from the S-A node reached the atria "after a delay which varies according to the duration of the preceding periods of rest." In an electrocardiographic study of one hundred children with scarlet fever, Wickström⁴⁷ observed three instances of this variety of S-A block. A similar example was described and analyzed by Lühr⁴⁸; the patient, an elderly man who had received large amounts of digitalis during the treatment of congestive heart failure, showed a varying four-to-three, five-to-four, and three-to-two block. Blumberger⁴⁹ discussed a single example of each type of S-A block, and later⁵⁰ reported a second instance of the Wenckebach type. Vedoya et al.⁵¹ reported four examples of S-A block, in three of which the sinoatrial conduction time increased progressively. Katz⁵² illustrated this phenomenon in his recent text.

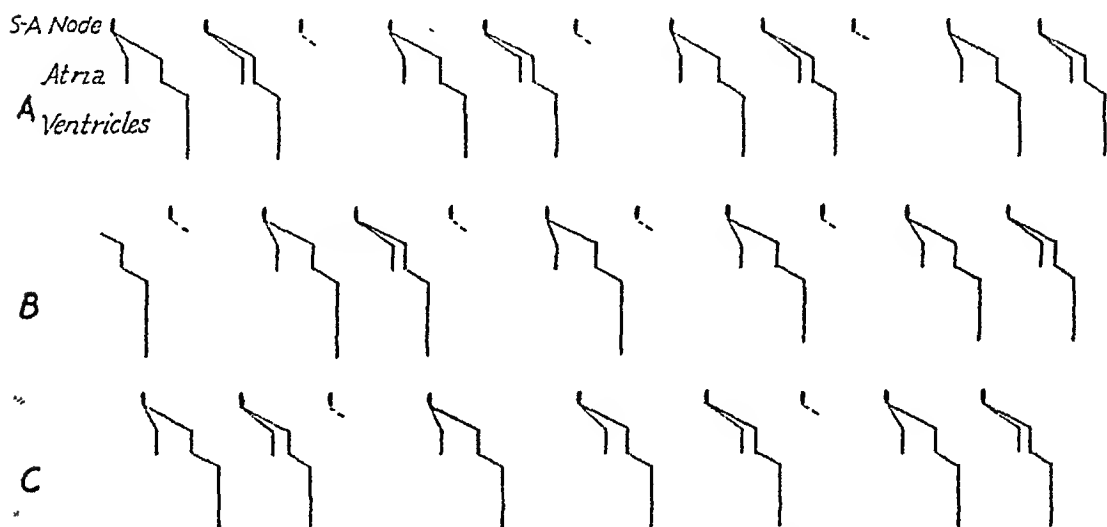


Fig. 3.—Diagrammatic representation of intracardiac conduction corresponding to the complexes shown in Fig. 2, A, B, and C. The usual mechanism is a three-to-two sinoatrial block, with the Wenckebach type of progressively increasing sinoatrial conduction time to the first atrial complex, and uniform conduction time to the second atrial complex until block appears. In line B there are two cycles of two-to-one block, and in line C a single cycle of four-to-three block.

It is probable that true complete block between the two atria, or between one atrium and the S-A node, exists in those reported cases of interatrial block that have shown two independent sets of P waves. On the other hand, what seems to be partial interatrial block may actually be partial sinoatrial block; Hertz' case³³ may be an example of this.

Careful measurements of the atrial complexes in our tracings show that the second negative complex (Fig. 2, Lead CF₂) occurs at a fairly regular rate of about 80 per minute (interval about 0.75 second), with each third beat usually dropped. This implies a three-to-two block between the S-A node and the atria. The same mechanism may also be assumed to explain the variable position of the first atrial complex of each pair; this concept is shown diagrammatically in Fig. 3. In this figure conduction from the S-A node to the two atria is represented by slanting lines, in the conventional manner, with the length of the lines and their angles roughly proportional to the conduction time.

The time at which S-A nodal discharge occurs must be, of course, entirely hypothetical. The conduction time from the S-A node to the (left?) atrium is shown to progressively increase, a behavior which is analogous to the Wenckebach type of A-V block. The conduction time to the (right?) atrium is uniform; A-V conduction time is constant until the block occurs. In each instance there is usually a three-to-two block; for a short period, Fig. 2, *B*, and 3, there is a two-to-one block; in the last line, Fig. 2, *C*, and 3, where there is transient slowing of the S-A nodal rhythm, the block is four-to-three. Thus, the assumption that the Wenckebach type of block is present between the S-A node and one atrium, and the Mobitz type of block between the node and the other atrium, logically explains the varying intervals of time between the two individual atrial complexes.

It is possible to measure tentatively the relative conduction times from the S-A node to the two atria. If the S-A nodal discharge is assumed to occur 0.01 second before the first of the two P waves, and if the conduction to the second atrial complex is uniform, increasing sinoatrial conduction times may be deduced for the three unpaired complexes of Fig. 2, *C*. These periods are 0.01, 0.11, and 0.17 second, respectively. Thus the greatest increase in conduction time is found in the second cycle of the group, a feature that is characteristic of the Wenckebach type of A-V block.

SUMMARY

Sinoatrial block of two types has been described; (1) with progressive prolongation of sinoatrial conduction time leading to a dropped beat; and (2) dropped beats without such preceding conduction changes. These are strictly analogous to the Wenckebach and the Mobitz types of atrioventricular block. The literature on this subject has been surveyed, together with available information on the postulated anatomic and functional pathways of inter- and intra-atrial conduction.

We have postulated that, in the present case, both varieties of sinoatrial block coexist, thus explaining the variable distance between the two types of P waves. Such a hypothesis also requires the assumption of functional pathways between the S-A node and the two atria, with dissociation of the two atria, and with partial dissimilar block between each atrium and the S-A node. Although interatrial dissociation, both partial and complete, and each variety of sinoatrial block have been previously described, so far as we have been able to learn, their coexistence has not been previously noted.

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Clinical Reports

SPONTANEOUS MEDIASTINAL EMPHYSEMA

A CASE REPORT DEMONSTRATING ELECTROCARDIOGRAPHIC CHANGES

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WITHIN a period of twelve months, three instances of mediastinal emphysema with and without pneumothorax came to our attention at an Army Station Hospital. The first was found in a soldier who some months previously had had a thoracotomy because of pulmonary abscess of the upper lobe of the left lung. Subcutaneous emphysema was present and was quite extensive. The second occurred during an attack of bronchial asthma in a patient with chronic asthma and was complicated further by left pneumothorax. The third example, which may properly be called spontaneous, in that no definite causative factor could be found, will be reported in detail.

We wish to add this case to the growing literature on this subject and, at the same time, to present an interesting electrocardiographic finding which we believe has not been demonstrated previously. Hamman¹ states that the electrocardiogram in mediastinal emphysema does at times show abnormalities, but that the changes are not marked. He has not observed the changes that we wish to report.

CASE REPORT

The patient, white, 40 years old, was a master sergeant with twenty-three years of Army service. He was hospitalized because of precordial pain. There was no history of familial or hereditary disease. Except for the usual childhood diseases, the patient had enjoyed perfect health. He had no serious illness or injury and had undergone no operation. On the day prior to hospitalization a sharp, stabbing pain which prevented deep inspiration had developed in the left lower side of the chest posteriorly. The pain gradually diminished and after seven hours ceased completely. The next morning the patient awoke feeling perfectly well. About 9:00 A.M., while at his desk, he was again seized with a severe pain in the left upper side of the chest and the tip of the left shoulder. The pain radiated to the left side of the neck and along the left costal margin. The pain was constant, was intensified by deep breathing, and was accompanied by profuse sweating. No other symptoms were present.

The patient was obviously in acute distress because of thoracic pain. The temperature was 97° F., the pulse rate 88 per minute, and the respirations 16 per minute. The blood pressure was 122/74. The patient was 73½ inches in height and weighed 150 pounds. Positive physical findings were present only in the anterior left side of the chest. In the supine position the heart sounds were barely audible. Adventitious sounds were present

but were limited to faint eliciting noises, synchronous with systole, over the precordium and along the left sternal border. When the patient assumed the sitting position, there was a marked increase in the abnormal sounds, which then became the typical crunching, crackling, popping noises which have been described as characteristic of mediastinal emphysema. In addition, the heart sounds became much more clearly audible and seemed to be normal in tone and character.

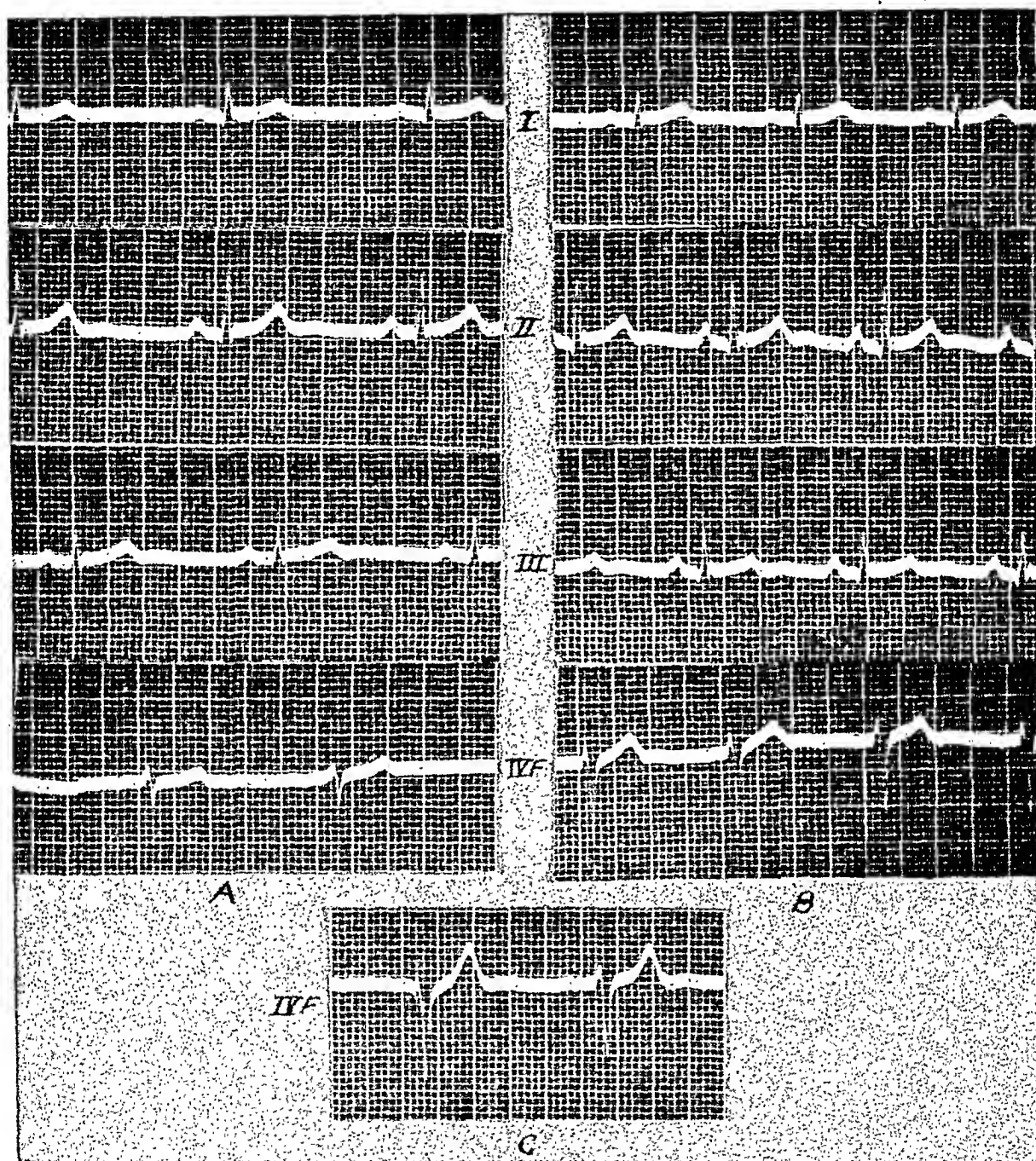


Fig. 1.—The tracings *A*, taken with the patient supine, and *B*, made in the sitting position, were obtained while mediastinal emphysema was present. The tracing marked *C* was made in the supine position after reabsorption of air from the mediastinum.

The laboratory reported no urinary abnormality, and the erythrocyte and leucocyte counts were well within normal limits. Roentgenographic examination of the chest in postero-anterior, lateral, and oblique projections revealed no evidence of pneumothorax or of air in the mediastinum. The heart was normal in size, shape, and position, and the lung fields were reported to be healthy. The electrocardiographic findings will be discussed later.

The pain subsided with bed rest and mild sedation. Treatment was entirely symptomatic, and all abnormal findings disappeared within nine days. The soldier then returned to duty, and when last seen, nine months later, reported that he had experienced no further difficulty.

An electrocardiogram was made on the third hospital day. Only the three standard limb leads were obtained, and these were normal except that the voltage was slightly lower than normal. On the sixth hospital day, electrocardiograms, including Lead IVF, were made with the patient both supine (Fig. 1, *A*) and sitting (Fig. 1, *B*). A comparison of these two tracings reveals practically no change in the limb leads. In the apical precordial leads, however, there are marked differences in voltage. In Lead IVF, taken with the patient supine, the voltage is definitely lower than normal, whereas in Lead IVF, made with the patient in the sitting position, the voltage is within normal limits. The total excursion of the QRS deflection of IVF taken supine measures less than 6 mm.; whereas in IVF taken in the upright (sitting) position the amplitude is 14 millimeters. The T waves present similar variations in voltage. On the ninth hospital day, when adventitious sounds could no longer be heard, a third tracing of Lead IVF was obtained with the patient supine (Fig. 1, *C*). This was practically identical with the tracing obtained three days previously with the patient upright. In an electrocardiogram made in the supine position nine months later, the limb leads did not differ from those shown in Fig. 1, *A* and *B*. The precordial lead of this later tracing was identical with the earlier precordial lead made in the supine position when physical signs were absent (Fig. 1, *C*). It was also identical with Lead IVF made in the sitting position when physical signs were present (Fig. 1, *B*). It does differ considerably from Lead IVF taken supine when the emphysema was present.

DISCUSSION

Hamman's original description of spontaneous mediastinal emphysema is contained in an article bearing the title "Remarks on the Diagnosis of Coronary Occlusion."² A few years previously, in a discussion entitled "Angina Pectoris," Wolferth and Wood³ described an instance of pneumothorax with precordial knock occurring after severe exertion. Recognition of the pathognomonic auscultatory finding, Hamman's sign,⁴ has done much to eliminate erroneous diagnoses, although mediastinal emphysema, when mild in degree and uncomplicated by either subcutaneous emphysema or pneumothorax, probably continues to go unrecognized.⁵ Moreover, intrathoracic vascular accidents are still confused with this condition and must be differentiated therefrom.^{6, 7} The first diagnosis in the case reported herein was coronary disease. This is readily understandable when one considers the rather sudden onset of precordial pain radiating to the left shoulder and side of the neck, the profuse perspiration and shocklike picture, and the very feeble faint heart sounds while the patient was in the supine position. The fact that x-ray examination failed to demonstrate air in the mediastinum or pleural cavities seemed to strengthen the original impression. However, the characteristic chest signs and the return of the normal heart tones when the patient assumed the upright position left no room for further doubt as to the correct diagnosis. It was the marked change in intensity of the heart sounds which change in posture which led to the taking of electrocardiograms in both the supine and sitting positions. The resultant wide discrepancy in voltage obtained in Lead IVF is clearly portrayed in Fig. 1.

The explanation which immediately occurred to us was a mechanical one. We thought that as the patient arose from the supine position the heart moved

anteriorly, this displaced the air in the anterior mediastinum and permitted the heart to come into contact with the anterior chest wall. This resulted in an accentuation of the crunching noises, and, as a result of the heart's being closer to the chest piece of the stethoscope, an intensification of the cardiac sounds. Conversely, when the patient reclined, the heart fell back, displacing air which had accumulated behind it, and allowed the air to return into the anterior mediastinum. This caused the heart sounds to become faint because a layer of air now separated the heart from the chest wall and stethoscope.

We believe the insulating effect of air in the anterior pericardial tissues is responsible for both the faintness of the heart sounds heard on auscultation and the low voltage in the electrocardiogram. It is known that the magnitude of the potential variations produced by the heartbeat at any point outside the heart itself diminishes rapidly as the distance from the epicardial surface increases.⁸ The interposition of air between the heart and the precordial electrode would not only increase the distance separating the two, but would also further reduce the magnitude of the potential variations, since air itself is a poor conductor of electricity. Wilson⁹ states that, in precordial tracings taken on patients with pneumopericardium produced after aspiration of fluid, the deflections are usually extremely small. Evidence to support the suggested mechanism of the changes observed in this case is found in the electrocardiogram obtained when all the mediastinal air had been reabsorbed, as determined by the disappearance of adventitious sounds and the return of the normal intensity of the heart tones with the patient supine. At this time Lead IVF (Fig. 1, C) was identical with Lead IVF obtained three days earlier with the patient in the upright position. The apical lead obtained nine months later with the patient in the supine position is also similar to the two mentioned previously.

This proposed explanation was submitted for comment to Dr. Frank N. Wilson, who graciously replied that with air between the precordial electrode and the heart one could probably expect findings similar to those observed in this case. Should it be found that other cases present the same, or similar, variations in physical and electrocardiographic findings with change in position of the patient, the changes we have described may prove to be of diagnostic importance, particularly in questionable cases in which pneumomediastinum is not demonstrable by roentgenography.

SUMMARY

1. A case of spontaneous mediastinal emphysema is reported.
2. Electrocardiographic changes not previously reported were observed. These changes are demonstrated.
3. The possible etiology of these changes is discussed.
4. Possible diagnostic value is ascribed to the findings which are described.

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PURE CONGENITAL PULMONARY STENOSIS

CASE REPORT

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PULMONARY stenosis in the heart without additional congenital defects is a rare occurrence. In a clinical and postmortem analysis of 105 cases of congenital heart disease by Gibson and Clifton¹ only two cases were found with uncomplicated pulmonary stenosis. The 1,000 cases of congenital heart disease analyzed by Maude Abbott² include only nine such cases. The bibliography of these cases was recently compiled by Bauer and Astbury³ who noted that the ages at the time of death were 10½ to 45 years with an average age of 22.8 years. Congenital pulmonary stenoses which allowed an average life expectancy of nearly 23 years were obviously not as marked or as severe in degree as the one to be reported here in which the opening in the stenotic valve was 2 mm. and the subject died of right-sided heart failure at the age of 11 months.

CASE REPORT

Mrs. G. consulted one of us (A. N. F.) about her 8-month-old daughter because, ever since birth, the following symptoms had been noted: (1) rapid and, at times, noisy breathing; (2) a heart rate that seemed faster than normal; and (3) extreme irritability. The mother related that this was her first child and that the birth had been perfectly normal. The family history was noncontributory. According to the mother, the infant was never blue. The patient took her feedings well but cried a great deal, in fact almost constantly, and for no apparent reason.

Physical examination revealed a well-developed and very well-nourished 8-month-old infant. There was moderate cyanosis. No dyspnea was evident. The respiratory rate was 24 per minute. The pulse rate ranged between 100 and 120 per minute. The lungs were clear to percussion and auscultation. Examination of the heart revealed a diffuse heaving impulse over the precordium. The apex impulse was in the fifth intercostal space at the left anterior axillary line. A systolic thrill was palpable over the pulmonic area. Auscultation revealed the presence of a loud, harsh, high-pitched systolic murmur, most intense in the second and third intercostal spaces to the left of the sternum, and transmitted to the left axilla and back. There was no clubbing of the fingers or toes.

A roentgenogram of the chest, taken when the child was 8 months old, revealed a marked increase in all cardiac measurements and an especially prominent pulmonary conus (Fig. 1).

An electrocardiogram, also taken at 8 months of age, showed sinoauricular tachycardia, a rate of 150 per minute, abnormally high P waves in all leads, very deeply inverted T waves in Leads II, III, and IVF, increased amplitude of QRS complexes, and a very marked right axis deviation (Fig. 2).

Clinical Course.—The infant was seen by us at various intervals and presented no change until she was 10 months of age. At this time the mother stated that she cried constantly, would not take her feedings, and vomited frequently. The infant now showed moderate edema of the upper eyelids and the cyanosis was more marked. There was dilatation of the external

jugular veins in the neck. The liver was enlarged and tender, its edge being palpable 3 finger-breadths below the right costal margin. The spleen was not enlarged. In spite of all therapeutic measures her course continued downhill. Edema soon appeared on the ankles and there was evidence of fluid accumulating in the abdomen. Two weeks before death a few moist râles appeared at both lung bases. The respirations gradually became more and more labored, and the cyanosis was more intense. At the age of 11 months, after suffering from right-sided heart failure for five weeks, the infant expired.



Fig. 1.

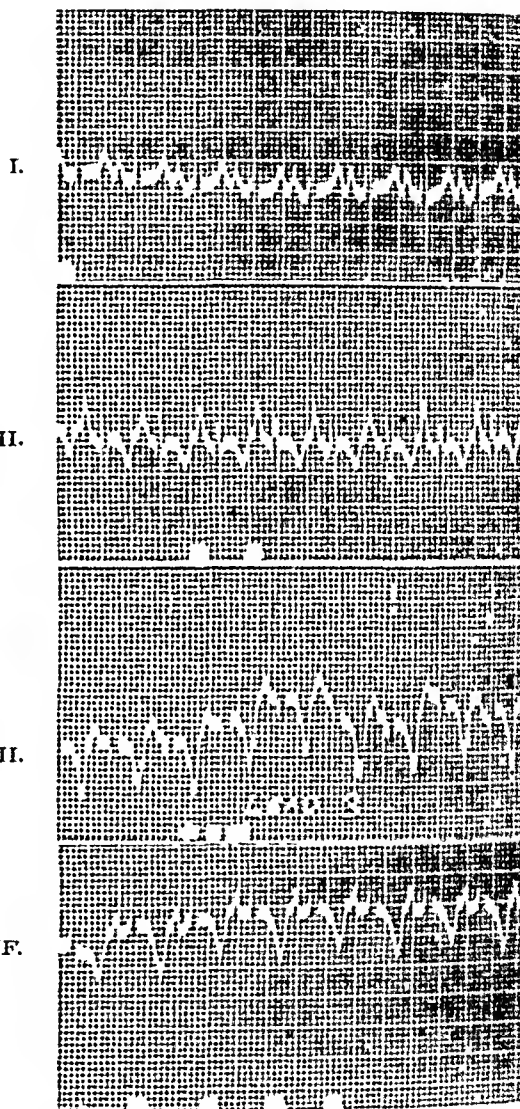


Fig. 2.

Fig. 1.—Roentgenogram taken at the age of 8 months. Note the generalized cardiac enlargement and the prominent pulmonary conus.

Fig. 2.—Electrocardiogram made at age of 8 months. Note the unusually high P waves indicating auricular enlargement; the marked right axis deviation and inverted T waves in Leads II and III indicating an enlarged right ventricle; and the high-voltage QRS complexes which are usually associated with increased mass of cardiac muscle.

Pertinent Autopsy Observations.—The pleural cavity contained a small amount of straw-colored fluid. The thymus was not enlarged. The lungs were voluminous and showed marked congestion throughout. There were no areas of consolidation. The heart (Fig. 3, A) weighed 102 grams (average normal for age: about 30 grams). The right auricle was greatly hypertrophied and dilated and measured 7 cm. in diameter. It had a smooth endo-



Fig. 3.—Note the enlarged right auricle and right ventricle in *A* and the greatly thickened myocardium in *B*. The pin-point opening in the pulmonary valve with its fused leaflets is demonstrated in *C*.

cardium. The foramen ovale was not patent. The tricuspid valve had a circumference of 3.5 cm., and its cusps were smooth and glistening. The wall of the right ventricle was greatly hypertrophied (Fig. 3, B), its thickness measuring 1.5 cm. at the base. There was no inter-ventricular septal defect. The pulmonary artery was found anterior to the aorta. The pulmonary valve showed complete fusion of its leaflets with only a pin-point perforation at the point of union (Fig. 3, C). This opening was only 2 mm. in diameter. The endocardial surface was smooth and glistening. The pulmonary artery was dilated for a distance of 2 cm. above the valve. The left auricle was small, measuring 2 cm. in diameter. The mitral valve had a circumference of 2.5 cm. and its cusps were smooth. The endocardium of the left ventricle was also smooth and glistening. The wall of the left ventricle measured 1 cm. at the base. The aortic valve showed no abnormalities and measured 2.5 cm. in diameter. The ductus arteriosus was not patent.

DISCUSSION

The most interesting feature of this case was the unusually small opening in the pulmonary valve which measured only 2 mm. in diameter. Such a small opening seems hardly compatible with life, especially when there was no other congenital defect through which the blood could be shunted. Yet this patient lived to be 11 months old and finally died of chronic right-sided heart failure which became clinically evident one month previously. The electrocardiogram and roentgenogram revealed corroborative evidence pointing to a heart in which the right cardiac chambers were preponderant. The tremendous effort required to force the blood through the narrow pulmonary opening was manifested by the great hypertrophy of the right ventricle. The mechanism involved in producing the hypertrophied right auricle is also clear; evidently it was caused by the increased work required to force blood into the ventricle which was already partially filled with blood. There was no evidence of any acute or chronic inflammatory reaction in the myocardium or endocardium, and the cause of fusion of the pulmonary leaflets has no rational explanation.

SUMMARY

A case of congenital pulmonary stenosis, with no other associated congenital defects of the heart, is reported. Death was caused by chronic right-sided heart failure at the age of 11 months.

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MYXOMA OF HEART

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PRIMARY myxoma of the heart is of sufficient rarity, and is associated with such diagnostic and therapeutic difficulties, that the reporting of an additional case is considered worth while.

CASE REPORT

C. C., a 35-year-old white housewife, was first seen in April, 1941, because of the sudden onset of paralysis of the left forearm. The past history and family history were irrelevant. Physical examination and neurological examination revealed nothing significant except the paralysis of the left forearm, which was of the upper motor neuron type. Laboratory findings and x-ray studies of the skull and chest revealed nothing abnormal. Physical therapy and supportive treatment resulted in some improvement.

She was admitted at intervals for the next year for study but no definite conclusions were reached. Over a period of months the paralysis improved slightly. She was last admitted Nov. 5, 1943. Her husband stated that a few hours previously she had awakened from sleep complaining of severe abdominal pain and had had an involuntary stool in bed.

On admission she seemed confused mentally. The abdomen was distended and tender in the lower quadrants. The lung fields were clear and the heart sounds were recorded as normal. The blood pressure was 110/80, the pulse was 100 per minute, and the respirations were 30 per minute. The paralysis of the left arm had not changed since the last admission.

The serology was negative. The erythrocytes numbered 4,500,000 per cubic millimeter, and the leucocytes numbered 9,200. The differential count was normal. The sedimentation rate was 27 mm. in forty-five minutes (Cutler). The spinal fluid was normal in all respects. A blood culture showed no growth at the end of twelve days.

A few days after admission the patient developed temperature elevations up to 104° F. The heart was found enlarged with the apex 13 cm. to the left of the midsternal line. A gallop rhythm was present. The heart sounds were "roughened," and there was a faint systolic murmur over the mitral area. Moist râles appeared in the lung bases with findings consistent with a hypostatic bronchopneumonia. The patient rapidly became worse and died Nov. 8, 1943.

Autopsy.—The significant findings consisted of a myxoma of the left atrium and numerous infarcts, of varying ages, of the brain, spleen, kidneys, and lungs.

The heart weighed 375 grams. Arising from a narrow base just below and posterior to the old foramen ovale was a soft papillomatous grayish pink tumor 7 cm. in diameter. It was composed of soft, rubbery, translucent tissue with numerous fingerlike processes that hung suspended through the mitral orifice. In the fissures between these processes were numerous thrombi. The cut surface of the tumor had a homogenous semigelatinous appearance. Elsewhere the endocardial surfaces were smooth and glistening, and the valve leaflets thin and pliable. The mitral valve ring appeared slightly dilated, measuring 11.5 cm. in circumference. The coronary arteries and aorta appeared normal. The lower lobes of the lungs were largely collapsed and airless. Scattered through the posterior aspect of both lungs were several recent infarcts which measured up to 2 cm. in diameter. The pleural surface of the infarcts was dark and bulging and the cut surface was dark red in color and

firm in consistency. The spleen weighed 275 grams, and scattered through the pulp were numerous infarcts measuring up to 2.5 cm. in diameter. These appeared of varying ages and had cut surfaces varying from a mottled yellow to a dark purplish red. The right kidney weighed 180 grams and the left weighed 220 grams. Both contained several infarcts measuring up to 3.5 cm. in diameter, some of which appeared of recent origin. The intervening parenchyma appeared normal. The brain weighed 1,350 grams. There was an irregular cortical atrophy of either parietal lobe, which was more marked on the right. There was a large area of old softening involving the operculum and the base of the precentral gyrus of the right hemisphere. This area was depressed and had a mottled yellow surface. The underlying brain substance showed softening with several small cystic cavities measuring up to 1 cm. in diameter. The blood vessels about the base appeared normal. The other organs showed nothing of significance.

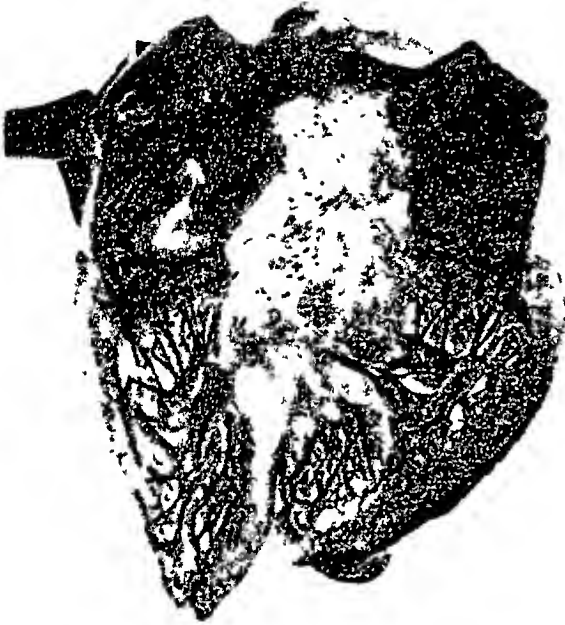


Fig. 1.—Left ventricle of heart showing tumor in situ.

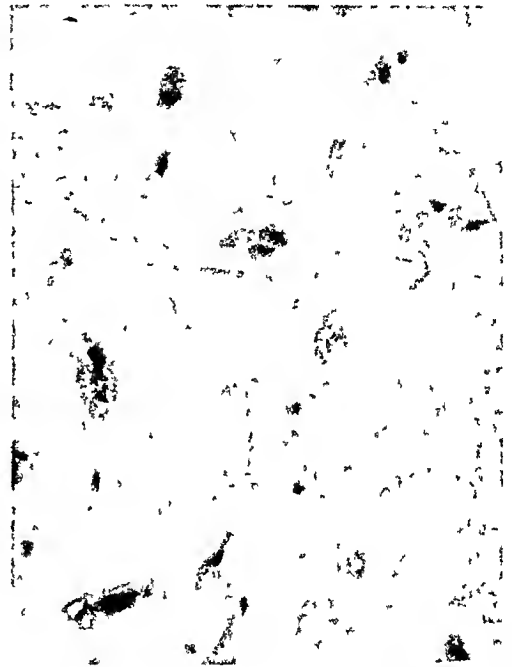


Fig. 2.—Tumor of left atrium. (X640.)

Examination of microscopic sections of the tumor of the left atrium showed it to have a relatively acellular structure composed of large stellate or polyhedral cells separated by a large amount of palely staining, faintly fibrillar or homogenous material. The cells had round, evenly chromatic nuclei and were frequently binucleated. The cytoplasm stained palely and was frequently drawn out into processes that seemed to merge with the stroma in many instances. The heart itself appeared normal. The old area of softening of the right cerebral hemisphere contained areas which had undergone liquefaction. These were surrounded by a zone of fibroblastic and glial proliferation with dense focal collections of gitter cells filled with ingested lipid material. Parts of the area were impregnated with old blood pigment, and the blood vessels of the vicinity had prominent cuffs of gitter cells. Scattered through both hemispheres were other minute scars having a similar structure, and interpreted as being on a similar basis. Sections of the lungs, spleen, and kidneys showed the usual changes of infarction. The other organs showed nothing of significance.

COMMENT

It is surprising that such a lesion as an intracardiac tumor of the size described here should not be associated with more obvious physical findings referable

to the heart. However, that such a state of affairs is not unusual with cardiac tumors is shown by previous contributions to the literature.^{1, 2} It should be noted, however, that the embolic phenomena which provided the only objective findings in the case reported here were not encountered in most of the other cases in the literature.³ That there was some interference with normal cardiac function might be inferred from the conspicuous cardiac hypertrophy, after allowing for the weight of the tumor, in the absence of hypertension, organic valvular disease, or arteriosclerotic changes. The sudden attack of abdominal pain which brought her to the hospital the last time might be explained by a sudden ischemia of a portion of the gut by an embolus which was too small to result in infarction, or which momentarily occluded the mouth of one of the mesenteric arteries, only to be carried on in the aorta to produce one of the renal infarcts.

While other types of tumors have been reported to arise in the heart,^{4, 5} myxomas account for the majority of primary benign tumors of the hearts of adults. Although other parts of the heart have been mentioned as the primary site, these tumors show a propensity for involvement of the left atrium, frequently in the region of the old foramen ovale,⁶ and, except for individual variations, present, a typical structure.^{7, 8}

Thorel⁹ has objected to the majority of reported primary myxomas of the heart and believes that they are organizing thrombi.⁹ There has been a notable tendency on the part of most of the authors of subsequent reports to accept metaplasia in an organizing thrombus as the probable pathogenesis of the tumors in their cases.¹² It seems germane to the question to remember that a myxoma is a specific oncologic entity and its normal tissue homologue is a differentiated but poorly specialized tissue. There seems to be no basis for assuming that repair processes such as organizing thrombi should give rise to myxomas within the cardiac chambers and not in the peripheral vessels, where most thrombi occur. The author has been unable to find any evidence indicating that thrombi in peripheral vessels ever terminate in myxomas. The cardiac ventricles, which are frequently the seat of thrombi, are practically never the site of myxomas. Moreover, the histologic structure of both myxomas and organizing thrombi should obviate confusing them.^{13, 14}

The occurrence of a fibromyxosarcoma and ulcerated lesions in the pulmonary artery led Haythorn and his co-workers,¹⁰ to postulate a probable origin of the tumor in their case from neoplastic changes originating in an organizing thrombus which developed over an atheromatous ulcer. Although thrombi do form over atheromatous ulcers, when encountered at autopsy they frequently appear recent, as though they had developed in the slowing circulation incident to the moribund state. The older ones commonly show central degeneration and liquefaction without any conspicuous attempt at organization.

It should be remembered that interference with the nutrition of the tissues, through the alterations characterizing atheromatosis, is a principal factor

*Ravid and Sachs,⁵ in calling attention to an error by Haythorn, Ray, and Wolff,¹⁰ quote Thorel⁹ as considering Bachmeister's case¹¹ to be "an edematous ball thrombus" instead of a true tumor. Such a reference cannot be found in Thorel's article, and actually Bachmeister's case came to necropsy two years after Thorel's article appeared in the literature.

underlying the production of an atheromatous ulcer. It seems questionable whether or not tissue so affected could support an active proliferative process. Finally, the occurrence of myxomas in otherwise normal hearts, in which there is no basis for assuming a pre-existing thrombus as in the case reported here, is additional evidence that cardiac myxomas are probably associated with thrombotic processes only as coincidental phenomena.

SUMMARY

The occurrence of a myxoma of the left atrium of the heart is reported. Embolic phenomena which have been rarely encountered in previously reported cases were most prominent in the clinical picture of this case. An attempt is made to evaluate the role of organizing thrombi in the pathogenesis of cardiac myxomas. The conclusion is they play little if any part in the development of such tumors.

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Letters

To the Editor:

My experience in over one hundred thousand examinations of the hearts of Merchant Seamen in a two and one-half year period is not in complete accord with the conclusions stated by Niehaus and Wright in their article, "Facts and Fallacies About the Normal Apex Beat," in the December, 1945, issue of the AMERICAN HEART JOURNAL.

The normal apex beat is seen in a minority of examinees at rest. The number may be increased by a lateral view in a good light.

The normal apex beat may be palpated in a majority of men without exercise. Contrary to the usual description of the apex beat, it is more often a subtle slight movement of a small area of the precordium than a definite thrust. The more sensitive the hand of the examiner, the more apex beats will be felt.

When examinees are subjected to a short period of exercise, and their precordia are palpated with the men bending forward and at the end of forced expiration, well over 90 per cent of apex beats may be palpated and a large number may be seen with the same technique.

The accuracy of these observations was tested by chest x-ray of every man and fluoroscopy of the doubtful cases. Percussion was a valuable though static and indirect check on the position of the apex beat.

Difficulty in palpating an apex beat was usually due to obesity or a thick chest wall in normal men, and occasionally in abnormal men to a flabby systole in a dilated heart. The effect of age on the apex beat was not evaluated.

(Signed)

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Feb. 14, 1946

To the Editor:

It is to be regretted that Dr. Quinn did not have his clinical assistants record his observation at the time each of his examinations was made. Such a record would have been formidable. He undoubtedly would have found that a critical analysis of his recorded facts of the "subtle slight movement of a small area of the precordium" could not have been identified in the majority of instances as a reliable first rate physical sign, even with a "more sensitive hand."

Physical diagnosticians differentiate between "an apex beat" and an "apex thrust." We must insist, however, that an apex beat has definite features, which are not too elusive.

Dr. Quinn's observation that the apex beat can be made more apparent by exercise, by bending forward, and by palpating at the end of the expiration seems valuable. However, this is not the usual method followed in eliciting this physical sign. In examining large groups under certain conditions it is conceivable that his modified, additional method would be valuable.

(Signed)

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March 5, 1946

Abstracts and Reviews

Selected Abstracts

Allen-Williams, G. M.: Pulse Rate and Blood Pressure in Infancy and Early Childhood. Arch. Dis. Childhood 20: 125 (Sept.) 1945.

An investigation of anthropometric methods which was carried out in municipal day nurseries at Oxford offered an opportunity for studying under standard conditions, the resting pulse rate and the ranges of blood pressure in healthy children, aged 6 months to 5 years.

The pulse rates were taken daily for a week during the afternoon rest hour when the children had been sleeping soundly for some time. The mean pulse rate per minute in children aged 6 to 12 months was 122 for males and 109 for females; in children aged 1 to 2 years it was 109 and 110, respectively. At 2 to 3 years of age the pulse rate fell to 100 among males and remained at this level up to 5 years of age. The mean pulse rate among females was found to decline regularly after they reached the age of 1 year, and at 4 to 5 years it was the same in both sexes. It was noted that there is a greater variation in the sleeping pulse rates of children in the same age group than there is in the daily sleeping pulse rate of the individual child.

Blood pressure was recorded very carefully from the right arm during the morning and only when the child was quiet and cooperative. The cuff had a width of 4 cm. for children under 2 years of age, 6 cm. for children 2 to 4 years of age, and 8 cm. for children 4 to 5 years of age. The mean blood pressures for males and females, respectively, were: at 6 to 12 months, 88/59 and 92/62; at 1 to 2 years, 96/66 and 95/65; at 2 to 3 years, 98/63 and 92/60; at 3 to 4 years, 99/66 and 99/64; and at 4 to 5 years, 99/65 and 99/66. There was an apparent tendency for systolic blood pressure to increase with age up to 4 years of age and to decline between 4 and 5 years of age. There was found to be a high correlation between the systolic and diastolic pressures, but no significant correlation between blood pressure and body weight in childhood. The author believes that his observations suggest a physiologic change in the circulatory system of children at the age of 2 to 3 years.

LAPLACE.

Burrows, A., and Stokes, W.: Mercurial Diuretics. Intolerance as Shown by Skin Sensitivity. Brit. Heart J. 7: 161 (Oct.) 1945.

Nine cases are reported in which skin erythema followed the administration of mercurial diuretics. Patch tests were made in all cases; this test is recommended as useful in determining the presence of sensitivity of the skin, especially when accumulation of the drug is suspected or when continuation of treatment is desirable after cutaneous sensitization.

The authors point out that many patients with sustained high dosage of mercurial diuretics show no signs of intolerance. Sensitization, idiosyncrasy, or allergy may be of different degrees. Skin rashes and itching, without other complications, would seem to indicate moderate sensitivity. There appears to be a threshold concentration of mercury in the blood, above which signs of allergy develop. This threshold may vary with the individual patient. Excessive dosage, poor diuresis, and renal impairment favor accumulation of the drug. The occurrence of cutaneous complications does not preclude further use of mercurial diuretics in adjusted dosage once the phase of sensitization is past.

LAPLACE.

Evans, W., and Lewes, D.: The Carotid Shudder. *Brit. Heart J.* 7: 171 (Oct.) 1945.

In nine patients in whom subsequent clinical, cardiographic, and cardioscopic examination established the presence of aortic stenosis and incompetence, the authors noted a characteristic sign which by itself permitted a diagnosis of the combined aortic lesion from inspection of the neck. This sign consisted of a momentary quiver or vibration which occurred at the height of the carotid pulse and was named the "carotid shudder." It is not found in all cases of aortic incompetence and stenosis but its presence is a sure indication of the dual lesion.

LAPLACE.

Cottrell, J. D., and Hayward, G. W.: The Effects of Emetine on the Heart. *Brit. Heart J.* 7: 169 (Oct.) 1945.

Changes in the electrocardiogram, blood pressure, and pulse rate produced by emetine and emetine bismuth iodide have been studied in soldiers under treatment for amebiasis. All were otherwise healthy, and the initial electrocardiograms were normal. Diminution or inversion of the T waves occurred in one or more leads in 25 of 32 patients receiving emetine and in 12 there was an increase in the P-R interval of from 0.02 to 0.04 second. Similar changes occurred during treatment with emetine bismuth iodide; seven of eight cases showed diminution in T waves and prolongation of the P-R interval. The cardiogram returned to normal eight to twelve days after completion of treatment. The effect on the blood pressure and pulse rate of both drugs was insignificant, and in no case was there any clinical evidence of myocardial insufficiency.

LAPLACE.

Gregory, R., and Levin, W. C.: Studies in Hypertension. V. Effect of High Spinal Anesthesia on the Blood Pressure of Patients With Hypertension and Far-Advanced Renal Disease—Its Possible Relationship to the Pathogenesis of Hypertension. *J. Lab. & Clin. Med.* 30: 1037 (Dec.) 1945.

Observations were made on the blood pressure changes produced by high spinal anesthesia in cases of hypertension with far-advanced renal disease. The study was dictated by the authors' belief that the elevated blood pressure of hypertensive patients with far-advanced renal arteriolar disease would not fall as much under spinal anesthesia as would the blood pressure of patients with hypertension and normal renal function under the same conditions if the initial blood pressure elevation were due to a humoral substance produced in the kidney. Twelve hypertensive patients with uremia, ten having essential hypertension, one acute glomerulonephritis, and one chronic glomerulonephritis, were studied. Their fall of blood pressure during spinal anesthesia was equal to that similarly produced in patients with essential hypertension and normal renal function. This result is considered evidence that even in patients with extreme irreversible arteriolar disease as shown by clinical and chemical evidence of uremia, the elevation of blood pressure is due to increased vasomotor tonus.

LAPLACE.

Wolf, R. E., Rauh, L. W., and Lyon, R. A.: The Prevention of Rheumatic Recurrences in Children by the Use of Sulfathiazole and Sulfadiazine. *J. Pediat.* 27: 516 (Dec.) 1945.

The authors report their experience with the effectiveness and reactions of sulfathiazole and sulfadiazine employed in groups of rheumatic children during the period of 1943 to 1945. The dosage used was sulfathiazole 0.5 Gm. twice daily or sulfadiazine 0.5 Gm. once daily.

There were no recurrences of rheumatic fever during treatment in a group of 70 children who received the drugs for a total of 81 patient seasons. One child developed subacute bacterial endocarditis while being treated and another developed it during the summer between treatment periods. One child developed rheumatic fever at the latter time. A few mild reactions occurred in the form of albuminuria, leucopenia, and skin rashes. These occasionally appeared as late as five months after inauguration of treatment. On the basis of this study, it appeared that this type of prophylactic therapy is safe and effective but should be con-

tinued throughout the year and sometimes for two years. The patient should have completely recovered from his infection before prophylactic treatment is started. LAPLACE.

Hines, L. E., and Kessler, D. L.: Ineffectiveness of Penicillin in Some Cases of Bacterial Endocarditis. *Quart. Bull., Northwestern Univ. M. School* 19: 296 (Winter Quart.) 1945.

There are many causes for the ineffectiveness of penicillin in the treatment of sub-acute bacterial endocarditis. The patient may die of valvular heart disease in the same manner as a patient who had never acquired bacterial endocarditis. Pathologic and clinical variations such as mycotic aneurysms, nephritis, myocarditis, cerebral embolism, and pulmonary infarction may be critical complications. Inadequate dosage of penicillin is often a cause of failure, especially in the presence of relatively insensitive organisms. Finally, penicillin itself may be harmful; practically no serious toxic effects have been reported, but allergic reactions are not rare. LAPLACE.

Naide, M., Sayen, A., and Comroe, B. I.: Characteristic Vascular Pattern in Patients With Rheumatoid Arthritis. *Arch. Int. Med.* 76: 139 (Sept.) 1945.

The basal vascular tone of a group of patients with rheumatoid arthritis was found to be high when studied by means of a test used for grading vascular tone. The test employed involved determination of the degree of vasoconstriction and vasodilatation as reflected in temperatures of the fingers and toes during a cool period and during the application of moderate heat to the trunk in a constant-temperature room at 20° C.

The high grade of vascular tone was present in the unaffected or the less affected digits or extremities so that this type of vascular response appears to be characteristic of individuals who develop rheumatoid arthritis. The tendency for the peripheral vessels in these patients to constrict easily may be one of the basic factors in predisposing them to rheumatoid arthritis and to flare-ups of the condition after emotional upsets and exposure to cold.

Subjects with early rheumatoid arthritis may have a dissociated type of temperature response to cold and reflex heat in their digital vessels which permits early diagnosis of the condition in some patients. NAIDE.

Gross, R. E.: Surgical Correction for Coarctation of the Aorta. *Surgery* 18: 673 (Dec.) 1945.

The author operated upon two patients with coarctation of the aorta following demonstration in dogs of the feasibility of removing segments of the thoracic aorta and re-establishing the arterial channel by end-to-end sutures of the vessel. In each of the two cases reported, the narrowed and obstructed part of the aorta was resected and the continuity of the vessel was then re-established. In both patients the anastomosis was satisfactorily completed but in the first patient, a 5-year-old boy, quick removal of the clamps resulted in the sudden opening of a huge vascular bed with immediate cardiac dilatation and death. In the second patient, a 12-year-old girl, the aortic clamps were removed very slowly over a period of ten minutes so that the cardiac and circulatory readjustments were brought about more gradually. In this patient, who survived, the pressure and pulsations in the lower extremities returned gradually until they were fairly normal by the seventeenth postoperative day. There was a concomitant decrease of the hypertension which had previously existed in the arms and upper portion of the body. NAIDE.

Tyson, M. D., and Goodlett, W. C.: Venous Pressures in Disorders of the Venous System of the Lower Extremities. *Surgery* 18: 669 (Dec.) 1945.

The authors measured the venous pressure in the lower extremities of patients with thrombophlebitis of leg veins. The normal venous pressure at the ankle with the patient

in the supine position and the table tilted so that the anterior surface of the foot was level with the auricles was found to be 2 to 9 cm. of water. When the femoral vein was occluded by a blood clot, the venous pressure at the ankle was elevated. In one such patient the venous pressure at the ankle of the affected leg was 49 cm., whereas on the unaffected side the venous pressure was 2 centimeters. Following ligation of the femoral vein the venous pressure at the ankle was 60.5 centimeters. In several of the patients, the high venous pressure declined gradually following femoral ligation as collateral circulation improved. The fall in venous pressure was attended by a corresponding reduction of edema. NAIDE.

Member, S., and Bruger, M.: Experimental Arteriosclerosis. VIII. The Effect of Feeding Olive Oil on the Absorption and Deposition of Cholesterol. Arch. Path. 40: 373 (Nov.-Dec.) 1945.

The authors found that when olive oil was added to the diet of rabbits in addition to cholesterol, the levels of blood cholesterol were slightly higher than when cholesterol was added alone. The deposition of cholesterol in the liver and the aorta was decidedly greater with the combination of olive oil and cholesterol than with cholesterol alone. NAIDE.

Grossman, C. M.: Pneumococcal Pericarditis Treated With Intrapericardial Penicillin, New England J. Med. 233: 689 (Dec. 6) 1945.

A case of pneumococcal pericarditis caused by Type VIII pneumococcus is reported. The patient was a man, aged 30 years, who was treated with penicillin which was administered parenterally and by intrapericardial injection. The first intrapericardial injection of penicillin consisted of 20,000 Oxford units. A second intrapericardial injection of 15,000 units was made thirty-six hours later. Recovery was uneventful. Although the intrapericardial administration of penicillin was not regarded as unquestionably responsible for the cure, the author believes that this procedure is warranted by the fact that the treatment of pleural and synovial infection is more successful when penicillin is used locally in addition to the parenteral route.

BELLET.

Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment. J. Thoracic Surg. 14: 347 (Oct.) 1945.

Two cases of coarctation of the aorta are reported in which surgical treatment was employed successfully. The patients were aged 12 and 27 years. The operation consisted of resection of the constricted part of the aorta and suture of the proximal and distal portions. The first operation was performed on Oct. 19, 1944, and the second on Oct. 31, 1944. Convalescence was uncomplicated in both cases. The patients were re-examined in March, 1945, and at that time were in excellent health and had returned to their former duties. Hypertension had been replaced by normal blood pressure. The blood pressure in the legs had likewise returned within the normal range.

The authors regard the operative results in these cases as evidence in favor of the mechanical theory of the cause of hypertension associated with coarctation of the aorta.

BELLET.

Wedd, A. M., and Blair, H. A.: The Action of Acetylcholine and Epinephrine on the Turtle Ventricle. Am. J. Physiol. 145: 147 (Dec.) 1945.

The action of acetylcholine on the turtle heart was investigated because in earlier work the refractory period was determined by a faulty method. The effect of acetylcholine on contractility was observed on ventricular strips suspended in a bath and stimulated rhythmically, the refractory period being determined from the Q-T interval of the electrocardiogram. Contraction height and diastolic length were decreased and the refractory period was slightly shortened. This action required much higher concentrations than those needed to produce the so-called inhibitory effects and was offset by atropine. It was believed to represent a direct action on myocardial fibers. The response to carbaminoylcholine ("Doryl") was found to be similar to that of acetylcholine.

The action of epinephrine on ventricular strips was studied in a similar manner. The results were strikingly irregular. The mechanically recorded contractions were at times increased and at other times decreased. The effect on the electrical responses of strips was likewise irregular, making it difficult to say that epinephrine has any definite influence on refractory period or conduction. LAPLACE.

Haney, H. F., and Lindgren, A. J.: The Effect of Acetylcholine on the Atropinized Denervated Heart. *Am. J. Physiol.* 145: 177 (Dec.) 1945.

This investigation concerns the possibility that acetylcholine exerts a direct stimulatory action on heart tissues or on ganglion cells within the heart, an action which is independent of and in opposition to its cardiodepressor influence. Dogs were subjected to removal of the stellate and upper five or six thoracic sympathetic ganglia and section of both vagus nerves. In three dogs, the adrenals were demedullated or denervated. At the beginning of each experiment, atropine sulfate, 2.6 mg. was given intravenously. The dogs were trained to lie quietly during the experiments. Acetylcholine was administered by venous infusion in doses of 1 to 4 mg. while the heart rate was recorded by means of the electrocardiogram. In 21 of 25 experiments on eight dogs, the heart rate increased more than 11 beats per minute with a maximum of 238 beats per minute. The time interval between the injection of acetylcholine and the onset of tachycardia was four to seven seconds. The brevity of this time interval is evidence in favor of the existence of a direct stimulatory action by acetylcholine either on the atropinized heart tissue or on intracardiac ganglion cells having a cardio-accelerator function. LAPLACE.

Ralston, H. J., Collings, W. D., Taylor, A. N., and Ogden, E.: Venous Return in the Absence of Cardiac Drive. *Am. J. Physiol.* 145: 441 (Jan.) 1946.

Venous return in the absence of cardiac drive has never been fully explained. Skeletal muscle tone has been regarded as an important factor. The phenomenon was therefore studied in acute experiments on dogs and cats by clamping the aorta and pulmonary artery and measuring the amount of blood which drained from the azygos vein. The amount of blood recovered in this procedure was 40 ml. per kilogram of body weight when light anesthesia was used, 27 ml. per kilogram of body weight when the animals were curarized, and 23 ml. per kilogram of body weight when dead animals, twenty-three minutes after experimentally induced ventricular fibrillation, was used. Control animals which were bled without arterial clamping yielded 46 ml. per kilogram of body weight. Thus a large proportion of the blood which can be drained from the azygos vein in the living animal with intact circulation can still be obtained after cardiac drive is eliminated. Splenic contraction appeared to contribute little if any blood to the total yield but skeletal muscle activity accounts, apparently, for about half the total yield. Elastic forces persistent in the tissues even after death may account for the remainder of the blood yield. LAPLACE.

MacNeal, Ward J., Blevins, A., and Poindexter, C. A.: Clinical Arrest in Enterococcal Endocarditis. *Am. J. M. Sc.* 211: 40 (Jan.) 1946.

Attention is called to the neglected recognition of *Streptococcus faecalis* as a cause of bacterial endocarditis. The authors estimate that it is the infecting organism in 10 to 15 per cent of such cases. They report the case of a man, aged 34 years, who had known valvular heart disease since 1927 and developed bacterial endocarditis late in 1943. Repeated blood cultures were positive for *Str. faecalis* and the organism was found to be rather resistant in vitro to the bacteriostatic action of neoarsphenamine, mapharsen, thiobismol, and penicillin; very resistant to sulfonamides; and quite susceptible to enterococcus bacteriophage. The patient was treated predominantly with thiobismol, penicillin, and bacteriophage for a period of nine months, followed by continued treatment with bacteriophage. The disease appears to have been arrested for a period of over a year. LAPLACE.

Gubner, R., Silvertone, F., and Ungerleider, H. E.: Range of Blood Pressure in Hypertension. J. A. M. A. 130: 325 (Feb. 9) 1946.

The current status of pressor and depressor tests in hypertension is reviewed, together with present concepts of the etiology of hypertension. The importance of knowing the maximum and minimum range of the blood pressure is emphasized. The authors recommend breath-holding or brief inhalation of spirit of ammonia as the most satisfactory method of obtaining the maximum pressor level, and hyperventilation combined with carotid pressure for obtaining the basal depressor level. Employment of these procedures makes it possible to differentiate humoral and neurogenic components in cases of hypertension. The authors believe that the neurogenic or vasomotor component is the important determinant in the initial elevation in blood pressure. In later stages, as the result of renal arteriosclerosis and ischemia, the renal pressor mechanism becomes involved. In older age groups arteriosclerosis of the medullary vessels with ischemia of the vasomotor system may be a contributing factor in heightened vasomotor pressor activity and hypertension.

NAIDE.

Cardozo, E. L., and Eggink, P.: Circulation Failure in Hunger Edema. Canad. M. A. J. 54: 145 (Feb.) 1946.

The circulation was studied in 29 cases of severe malnutrition. Characteristic features were a slow pulse rate, ranging from 40 to 50 per minute, a low blood pressure with systolic levels under 100 mm., and a low pulse pressure. The circulation time (using 10 per cent magnesium sulfate) was prolonged; in 76 per cent of the patients it was more than 20 seconds and in the more serious cases it was more than 30 seconds. The circulation time was increased in the absence of apparent evidence of heart failure. The electrocardiograms showed low voltage and bradycardia. Roentgenography failed to reveal evidence of any cardiac enlargement. The basal metabolic rate ranged from -20 to -40 per cent. The serum protein level was low, particularly the albumin fraction. The hemoglobin averaged between 60 and 70 per cent.

BELLE.

Logue, R. B., and Hanson, J. F.: Electrocardiographic Changes Following Heat Stroke. Ann. Int. Med. 24: 123 (Jan.) 1946.

A case is reported in which significant electrocardiographic changes occurred during heat stroke. The authors found relatively few similar reports in the literature, although the cardiac complications of heat stroke have been generally recognized and consist of dilatation of the right ventricle and subendocardial hemorrhages. In experimental heat stroke, various arrhythmias have been produced. In the present case, the electrocardiographic changes consisted of inversion of the T waves in all leads, with slight S-T segment deviation. These changes disappeared during a period of two and one-half months. It is pointed out that the cause of the electrocardiographic changes is uncertain, since the patient was in profound shock and digitalis had been administered for twenty-four hours prior to the first electrocardiogram.

BELLE.

Loewe, L., Plummer, N., Niven, C. F., Sherman, J. M.: Streptococcus s.b.e. in Subacute Bacterial Endocarditis. J. A. M. A. 130: 257 (Feb. 2) 1946.

An apparently new variety of nonhemolytic streptococcus was isolated in 41 (39 per cent) of a series of 106 consecutive blood cultures from cases of subacute bacterial endocarditis. The organism was designated *Streptococcus s.b.e.* Its cultural properties, relationship to other streptococci, and serologic classification were studied in detail. Its refractory character was strikingly apparent from a comparative study of treatment statistics, recovery percentage, mortality rate, and incidence of recurrence. Intensive, massive penicillin treatment was found to be mandatory in order to terminate the disease in patients affected with *Streptococcus s.b.e.* The optimum dosage of penicillin was an uninterrupted span of treat-

ment for eight weeks with daily intravenous administration of at least 2 million Oxford units. The prompt identification of this organism as the causative agent in subacute bacterial endocarditis facilitated by the use of the presently available diagnostic serum has been a lifesaving measure. BELLET.

Smolik, E., Blattner, R. J., and Hays, F. M.: Brain Abscess With Congenital Heart Disease. J. A. M. A. 430: 145 (Jan. 19) 1946.

The authors regard the association of brain abscess with congenital heart disease as being insufficiently emphasized in the literature and report a case of this type. The patient was a girl, aged 9 years, whose cardiac lesion was either a patent ductus arteriosus or an interventricular septal defect. Symptoms suggestive of brain abscess developed and the diagnosis was established by ventriculography. Surgical drainage of the abscess was followed by complete recovery. Penicillin and sulfonamide therapy were maintained during convalescence. The organism cultured from the aspirated pus was identified as a member of the *Haemophilus influenzae* group.

It is pointed out that the ante-mortem diagnosis of brain abscess in patients with congenital heart disease is uncommon and that the diagnosis could be made more frequently if the possibility of this association is borne in mind. BELLET.

Robertson, H. F., Schmidt, R. E., and Feiring, W.: The Therapeutic Value of Early Physical Activity in Rheumatic Fever, Preliminary Report. Am. J. M. Sc. 211: 67 (Jan.) 1946.

Confinement to bed is not regarded by the authors as necessarily affording optimum rest, especially in cases of acute rheumatic fever where prolonged confinement tends to produce restlessness and to develop a psychoneurosis. The therapeutic value of early ambulation in rheumatic fever was therefore studied in a series of two hundred cases. The patients were placed on a regime in which comfort was the sole factor in determining the extent of permitted activity. All patients except those who had heart failure or incapacitating joint inflammation were allowed to use the latrine during the first twenty-four hours, and thereafter they were permitted to sit up in a chair for increasing intervals. As strength returned they were allowed to walk about the hospital. Joint discomfort very rarely prohibited ambulation for more than forty-eight hours when adequate amounts of salicylate were given. Tachycardia, cardiac murmurs, heart block, subcutaneous nodules, moderate joint pains, rapid sedimentation rates, abnormal electrocardiograms, or other laboratory findings indicative of active rheumatic fever or carditis were not used as indications for confinement.

No unfavorable effects of this treatment were noted, while, on the other hand, the advantages included marked decrease in the incidence and severity of anxiety neuroses, sounder sleep, improved bowel function, decreased abdominal pain, improved appetite, and gain in weight. In the majority of cases the manifestations of acute rheumatic fever disappeared during the period of physical activity. The success of this type of treatment invites attention to re-evaluation of the currently accepted policy of prolonged bed rest with its disadvantages in the management of acute rheumatic fever. LAPLACE.

Bloomfield, A. L., and Halpern, B. M.: The Penicillin Treatment of Subacute Bacterial Endocarditis; Some Problems. J. A. M. A. 129: 1135 (Dec. 22) 1945.

A series of eighteen consecutive cases of subacute bacterial endocarditis is reported in which penicillin therapy was employed and the infection has been arrested for periods of three to seventeen months. Bacterial and clinical arrest in 100 per cent of this series is contrasted with the arrest of only 50 to 75 per cent in the series of more briefly treated cases reported in the literature.

An important criterion for determining the dosage of penicillin necessary to obtain a favorable response was the strain sensitivity of the organism. If more than 0.1 Oxford unit of penicillin per cubic centimeter of medium was required for complete inhibition of growth,

the case was likely to be refractory to the amount of treatment usually given and doses up to 1 million Oxford units per day might be necessary.

In order to obtain the highest percentage of cures, treatment should be continued for two months and in some cases longer. If the strain is sensitive, the best treatment consists of a total daily dose of at least 200,000 units administered in four to eight intramuscular injections. In the presence of more resistant strains, very large doses of 500,000 units or more of penicillin may be necessary to obtain a cure.

Subcurative therapy may produce not only deceptive pseudocures with return of bacteremia as soon as treatment is stopped, but also a more resistant strain of streptococci. It is important to recognize the infection early so that treatment may be started before excessive heart damage has occurred.

BELLET.

Wheeler, E. O., and White, P. D.: *Insomnia Due to Left Ventricular Heart Failure.* J. A. M. A. 129: 1158 (Dec. 22) 1945.

Insomnia as a presenting symptom of left ventricular failure has been generally neglected. When dyspnea is not a prominent complaint, however, insomnia may be the predominant symptom of pulmonary congestion. In such cases, the patient may be inadequately treated because of failure to recognize the underlying heart disease. Treatment with digitalis and diuretics and restriction of salt result in improvement of heart function and relief of the insomnia.

BELLET.

Iokhveds, B. I.: *Intracardiac Blood Transfusion.* Am. Rev. Soviet Med. 3: 116 (Jan.) 1946.

Intracardiac blood transfusion is recommended only for patients who are moribund. Two cases are reported in which the blood was introduced directly into the ventricles. The transfusions were given respectively eight and ten minutes after clinical death. In one patient the injection was made into the right ventricle and in the other patient into the left ventricle. Use of the left ventricle is preferable, particularly when the moribund state is the result of severe hemorrhage, as in one of the cases reported. Three advantages for left-sided transfusion are cited: (1) The increase in the contents of the left ventricle acts as an impulse to start contraction. (2) Even the first comparatively weak contractions of the heart partially re-establish the blood supply to the brain centers. (3) The left ventricular route immediately improves the coronary blood supply. The use of the right ventricle for transfusion has been previously reported, but the author has found no previous reference to the use of the left ventricle for this purpose.

McMILLAN.

Connell, W. F., Wharton, G. K., and Robinson, C. E.: *The Relationship of Blood Pressure and Serum Thiocyanate.* Am. J. M. Sc. 211: 74 (Jan.) 1946.

The purpose of this investigation was to ascertain whether there is any correlation between the height of the blood pressure and the amount of thiocyanate in the blood serum of persons who have not received thiocyanate therapeutically. In 341 subjects whose blood pressures ranged from hypotensive levels averaging 99/61 to hypertensive levels averaging 228/131, a substance giving the color reaction of thiocyanate was found in the serum in concentrations of 0 to 2.77 mg. per 100 milliliters. No correlation was found between the serum concentration of this substance which was estimated as potassium thiocyanate, and the height of the diastolic blood pressure. It is concluded that, if thiocyanate actually does occur normally in the blood serum, it has no role in the regulation of blood pressure.

LAPLACE.

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Original Communications

USE OF THE PHLEBOMANOMETER: NORMAL VENOUS PRESSURE VALUES AND A STUDY OF CERTAIN CLINICAL ASPECTS OF VENOUS HYPERTENSION IN MAN

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PHYSIOLOGISTS have long considered a knowledge of the variations in venous pressure essential to the proper understanding of cardiovascular physiology.^{1, 2} More recently some clinicians have utilized venous pressure measurements in the differential diagnosis and clinical management of right ventricular congestive heart failure, pericardial effusion, constrictive pericarditis, cardiac tamponade, localized venous obstruction, edema, ascites, and many other clinical syndromes.³⁻⁸ Measurements of venous pressure, however, are not often made routinely by those in the clinical fields. Furthermore, progress in a proper understanding of the pressure in veins has been retarded by many factors, principally a need for a simple, practical, portable instrument and a standardized method of recording venous pressure; and an appreciation of the clinical applications of venous pressure measurements. To date no completely satisfactory instrument for the measurement of venous pressure has been found. Such instruments have been impractical, or inaccurate, or both. A satisfactory instrument must, at least, be (1) portable, transportable, with no fluids to spill, and suitable for bedside use in the hospital or home; (2) easily sterilized and easily prepared for successive determinations; (3) suitable for use in small veins, thereby making possible comparative measurements as well as a more general use; and (4) sufficiently accurate and dependable to reveal early evidence of or change in disease.

Since a standard method of recording the venous pressure has not yet been accepted generally, values obtained by different methods are not always comparable.⁹ The site taken as "heart level" varies with the various methods used.

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Any variation of this site often produces considerable differences in the results obtained. The criteria for a satisfactory heart level are discussed. Because a knowledge of the venous pressure is of diagnostic assistance in many disease states,¹⁰ it is the purpose of this report to describe in detail the technique employed with the Phlebomanometer,¹¹ to discuss some of the factors affecting venous pressure, to establish a phlebotatic level and a phlebotatic axis,¹² to establish normal values of venous pressure for adults, and to present studies on patients with venous hypertension in congestive heart failure.

METHODS AND MATERIAL

The instrument used was the Phlebomanometer,¹¹ which consists of an aneroid type of manometer, the scale of which is calibrated in millimeters of water. The method is a direct one. By mechanically compressing a pressure bulb the pressure in the manometer system is adjusted to balance the pressure in the vein. When the balance has been accomplished the venous pressure is read from the scale of the manometer. The balance is established when a column of citrate solution in a glass adaptor comes to rest. The capillarity of the adaptors (1-mm. bore) used was 25 mm. of 2 per cent citrate solution. To correct for capillarity, the meniscus of the citrate in the adaptor was held 2.5 mm. above the level of the vein. A 23-gauge needle was usually employed, although the size of the needle did not alter the venous pressure reading, since the reading is recorded when the fluid in the adaptor is at rest. Smaller-bore needles were used when measuring high venous pressures. The Phlebomanometer conforms to the criteria established for a satisfactory venous pressure instrument.¹¹ It was checked at frequent intervals against a water manometer and was found to maintain its accuracy at all times.

Approximately 850 determinations were made on 200 normal subjects, and 450 determinations were made on 90 patients with cardiac disease. The normal subjects were medical students and laboratory and hospital attendants. The patients were selected from the medical wards of the Charity Hospital in New Orleans.

The subjects rested ten minutes before venous pressure determinations were recorded. In all instances consecutive readings were taken until constant readings were obtained. Particular attention was paid to the state of relaxation of the patient, the type of respiration, and the maintenance of the vein at "heart level." All determinations on normal subjects were carried out on an unpadded, level examining table with the arm abducted, slightly rotated externally, and properly supported. When the veins of other parts, such as the foot or hand, were studied, these parts were similarly supported in a relaxed state so as to avoid venous obstruction due to flexion of joints, external pressure, or constriction.

REFERENCE LEVEL OR HEART LEVEL

In order to obtain reproducible venous pressure readings, the vein under study must be placed in a constant relation to the heart. The phlebotatic

level¹² has been used as a reference level. It has the advantage of being applicable for use in positions other than the supine. It may be defined as a horizontal plane passing through the phlebostatic axis.¹² The axis is determined by the intersection of a frontal plane, passing half the distance from the base of the xiphoid of the sternum and the dorsum of the body, with a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. The use of the *phlebostatic level* of reference gives reproducible and comparable results in normal subjects when either supine, in the intermediate sitting positions or in the upright sitting position.¹² The following experiments are described in order to emphasize the practicability and reliability of the phlebostatic level as a reference level for these positions.

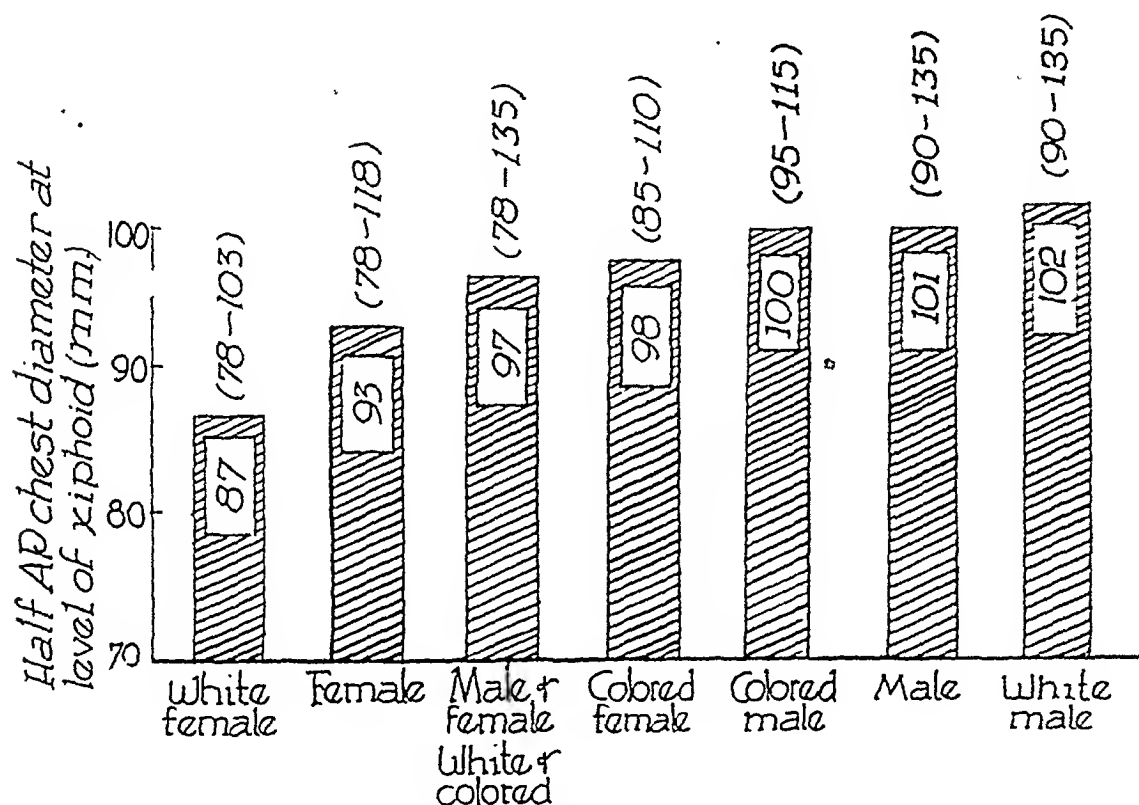


Fig. 1.—Half the anteroposterior diameter of the chest, measured from the base of the xiphoid to the table with the subject in the supine position, in 90 Negro and white males and females. A horizontal plane passing through this point forms the phlebostatic level for the supine position.

The Phlebostatic Level.—Half the distance from the base of the xiphoid to the table with the subject supine (phlebostatic level for the supine position) was measured in 90 normal subjects from 16 to 34 years of age (Fig. 1). The venous pressure was taken in the median basilic vein with the vein at this level. The subjects were divided into those with deep chests and those with thin chests. The ages, sexes, and colors of the two groups were comparable. The venous pressure did not vary significantly in the two groups.¹² The narrowest chests occurred in the white female group (average, 87 mm.; extremes, 78 to 103 mm.) and the deepest chests occurred in the white male group (average, 102 mm.; extremes, 90 to 135 mm.). The average depth of the chests for males and females of both colors was 97 mm. (extremes, 78 mm. and 135 mm.).

The influence of chest thickness on the venous pressure, using the phlebostatic level with the subjects in the supine position, was further tested in 10 subjects with very thick chests (average, 126 mm.; extremes, 110 to 135 mm.), and 10 with very thin chests (average, 89 mm.; extremes, 85 to 95 mm.) (Fig. 2). The venous pressures in the median basilic vein were 103 and 104 mm. of water, respectively. Thus even extremes of chest thickness did not materially influence the venous pressure measurements.

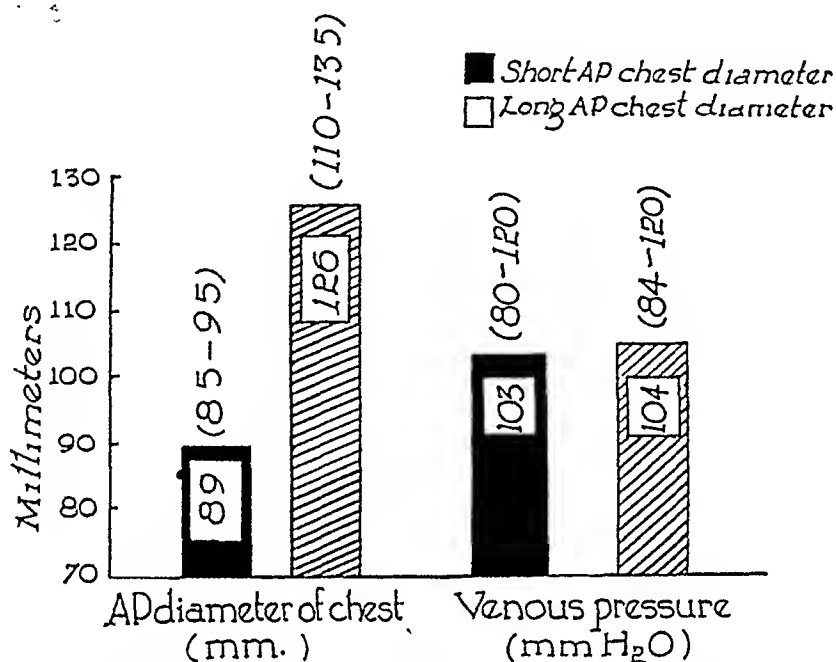


Fig. 2.—The venous pressure measured in 10 subjects with thick chests and 10 of the same sex, age, and color with thin chests. The venous pressures show no significant differences.

Venous pressures were then recorded for the median basilic vein in 13 subjects, first in the supine position, and then in the upright sitting position, the arm being raised until the pressure in the sitting position was the same as that in the supine position. In eight of the 13 subjects the vein under study fell in a horizontal plane which passed through the fourth intercostal space adjacent to the sternum. In the remaining five subjects, the vein fell either in the third or fifth intercostal space. Placing the trunk in various intermediate sitting positions and measuring the median cubital venous pressure with the vein in a horizontal plane passing through the phlebostatic axis resulted in little difference in values among normal subjects.¹² The reliability of the phlebostatic level was further tested by recording the venous pressure in a dorsal vein of the hand, with the trunk in the supine position, various intermediate sitting positions, and in the upright sitting position (Fig. 3). In all positions the hand was kept at the phlebostatic level for the supine subject. With each change of position the venous pressure increased by an amount equal to a column of blood extending from the vein under study to the phlebostatic level. Thus the phlebostatic level is a genuine physiologic level of reference.

Radiographic studies indicated that in the majority of subjects the phlebo-static axis passed through the posterior aspect of the right auricle. Thus the anatomic and physiologic reference levels coincide satisfactorily, and the phlebo-static level is a satisfactory reference level for the measurement of venous pressure for the supine position, intermediate sitting positions, and upright sitting positions.

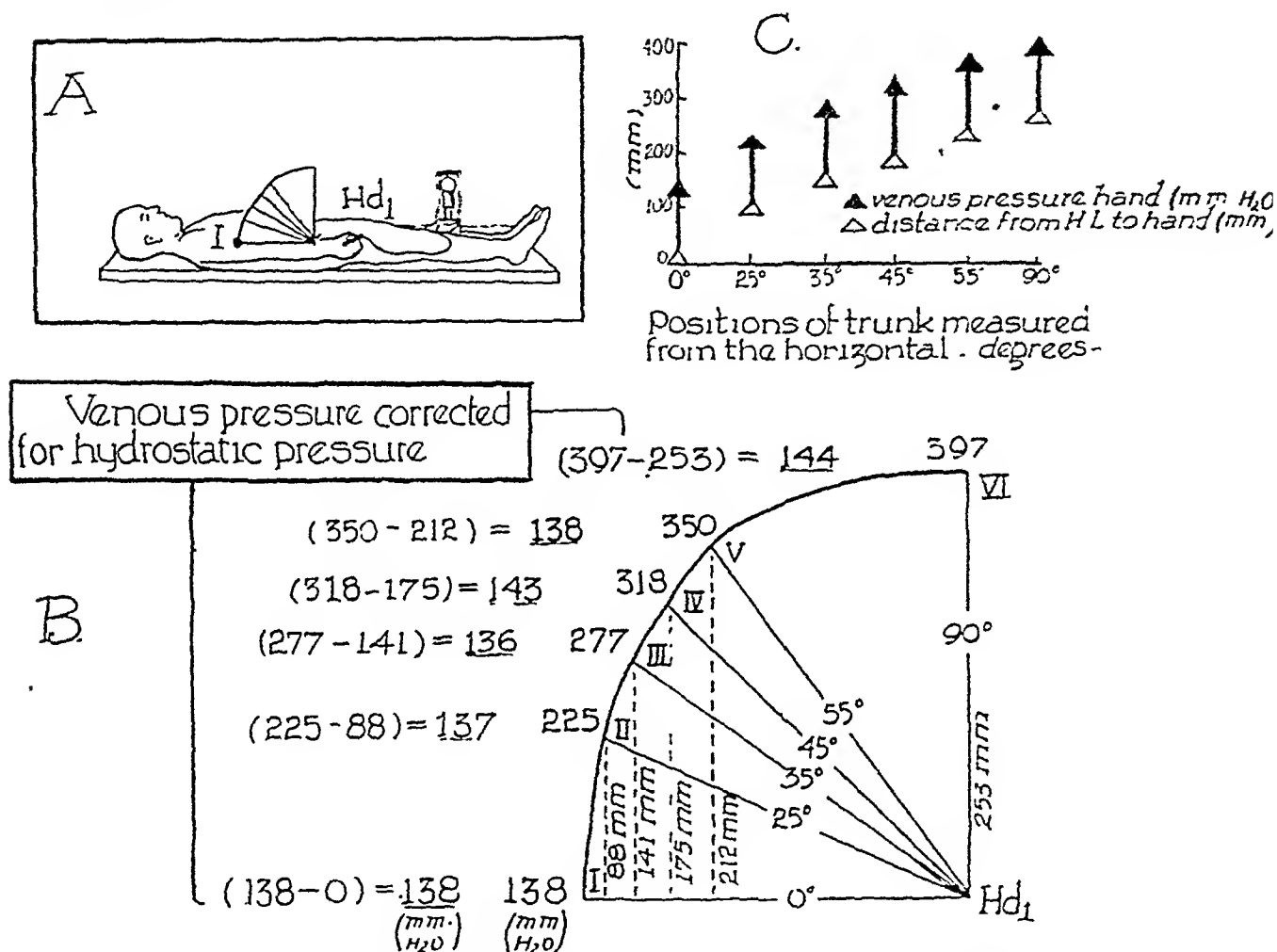


Fig. 3.—The phlebo-static axis used as heart level in the supine, various intermediate sitting, and upright sitting positions. A, Subject in supine position and hand (Hd) in a horizontal plane passing through phlebo-static axis (solid dot). B, Venous pressures corrected for hydrostatic pressure resulting from the elevation of the phlebo-static axis to Positions II, III, IV, V, and VI, leaving the hand in which the venous pressure determination is being made in position Hd. C, Proportional increase in venous pressure and hydrostatic pressure with each change of trunk position. The phlebo-static level is a useful reference level for subjects in the supine, intermediate sitting, or upright sitting position.

FACTORS AFFECTING VENOUS PRESSURE

Numerous factors which affect the venous pressure must be evaluated and understood if errors in venous pressure measurements are to be avoided. A knowledge of such factors is of clinical importance when measuring venous pressure.

Relation of Venous Pressure to the Phlebo-static Level.—The venous pressure was determined in the median basilic vein at the phlebo-static level in 10 subjects in the supine position. The vein was raised above and lowered below

this level and the changes in pressure were recorded. Raising the arm 100 mm. above the level reduced the pressure 100 mm. of water. Lowering the arm 40 increased the pressure 40 mm. of water. This 1:1 relationship was constant, at least for positions between 40 mm. below and 100 mm. above this level. This relationship between the phlebostatic level and the position of the vein is probably maintained for ranges wider than those studied. Thus, when venous pressure is measured in veins above or below this level a simple correction may be applied for the altered hydrostatic pressure due to the position of the vein.

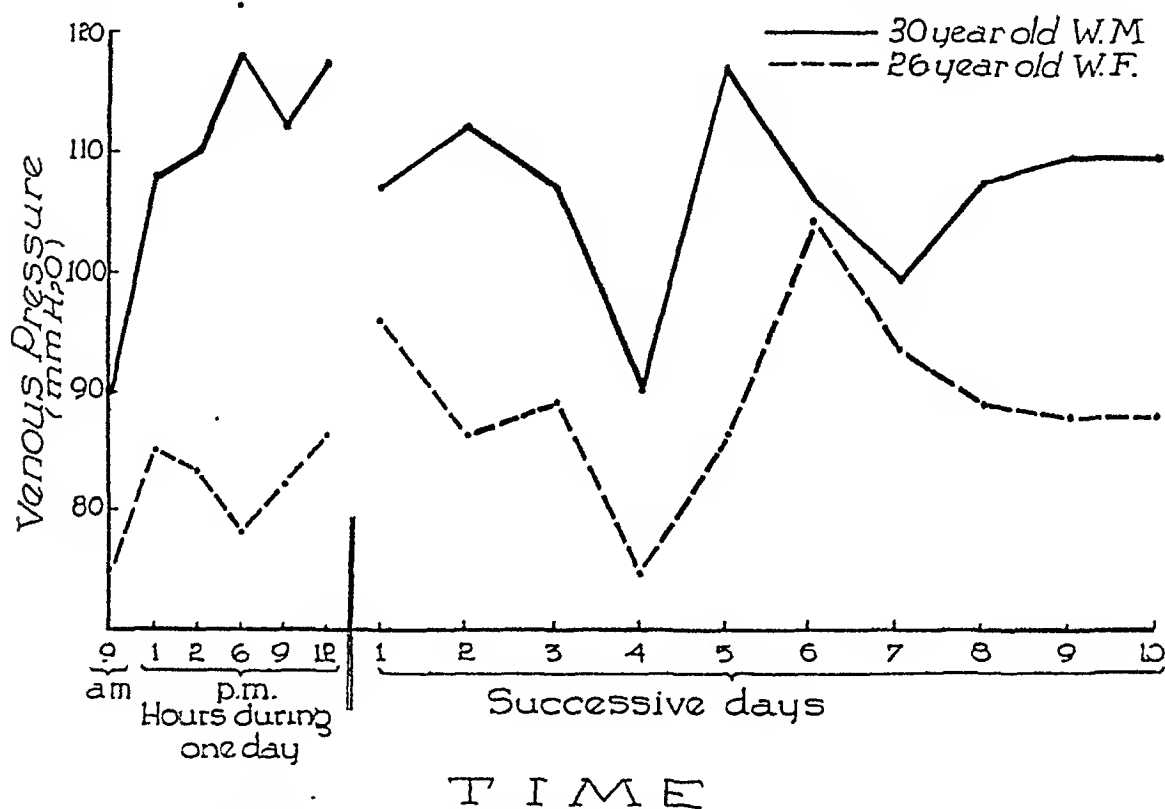


Fig. 4.—Variations in venous pressure during one day and at the same time of day for ten consecutive days.

Venous Pressure Variations During One Day and From Day to Day.—Venous pressure was determined in the median basilic vein in one man and in one woman at three-hour intervals from 9:00 A.M. to 12:00 M. throughout one day, and once daily at the same hour for ten days (Fig. 4). The error in consecutive readings was no greater than ± 2.5 mm. of water. The venous pressures were generally lower in the woman than in the man. Both subjects had lower pressures in the morning than in the evening, the morning pressure being 11 mm. lower in the woman and 27 mm. lower in the man. There was no constant relationship between the venous pressure level and meals.

Ten consecutive daily recordings were made at 11:00 P.M. for ten days. The daily activity of the subjects did not vary significantly during this period. The difference between the highest and lowest readings was 29 and 27 mm. of water in the woman and the man, respectively.

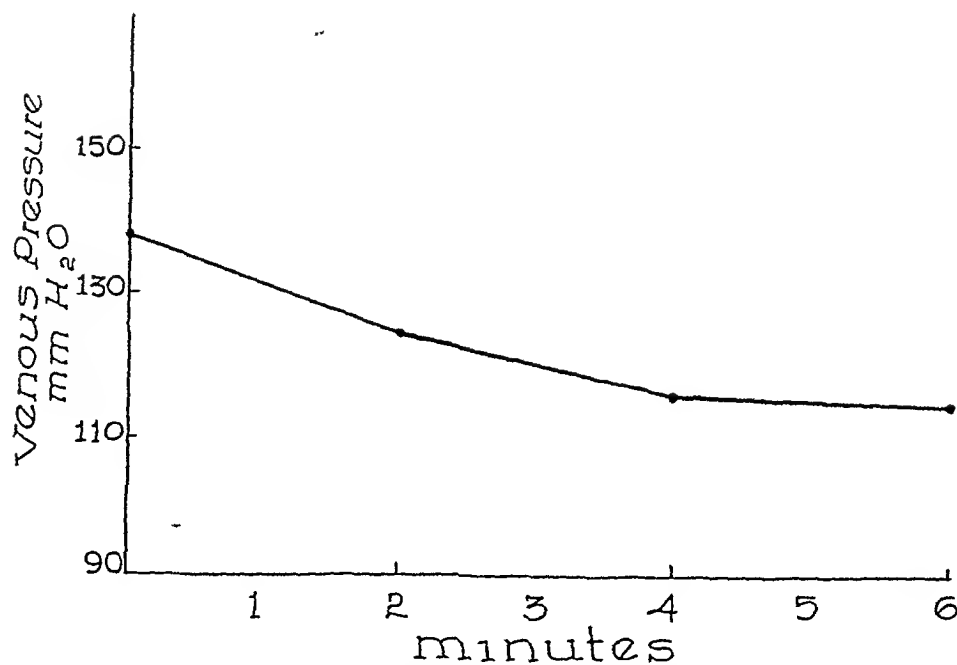


Fig. 5.—The gradual fall in the venous pressure of 20 subjects after insertion of the needle ordinarily occurred during the first four minutes.

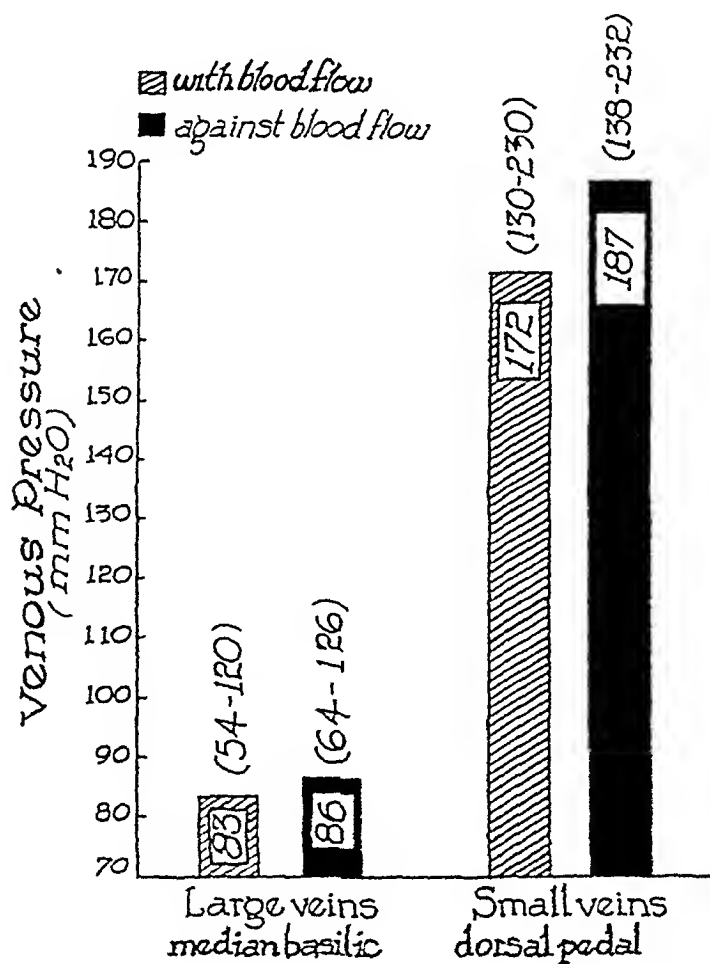


Fig. 6.—Pressures determined in large and small veins with the needle directed in and against the direction of blood flow. Pressure differences were greater in the small veins, probably because of the greater effect of venous spasm in small veins.

Venous Pressure Drift.—The venous pressure was usually high immediately after the vein was punctured, and lower after the needle had remained in place for a period of time. In the 20 subjects studied, the pressure was usually constant by the fourth minute (Fig. 5). The average decrease in pressure was 20 mm. of water. This change in venous pressure took place without apparent muscle tension or changes in respiration. Spasm of the vein was usually directly visible, particularly in the smaller veins.

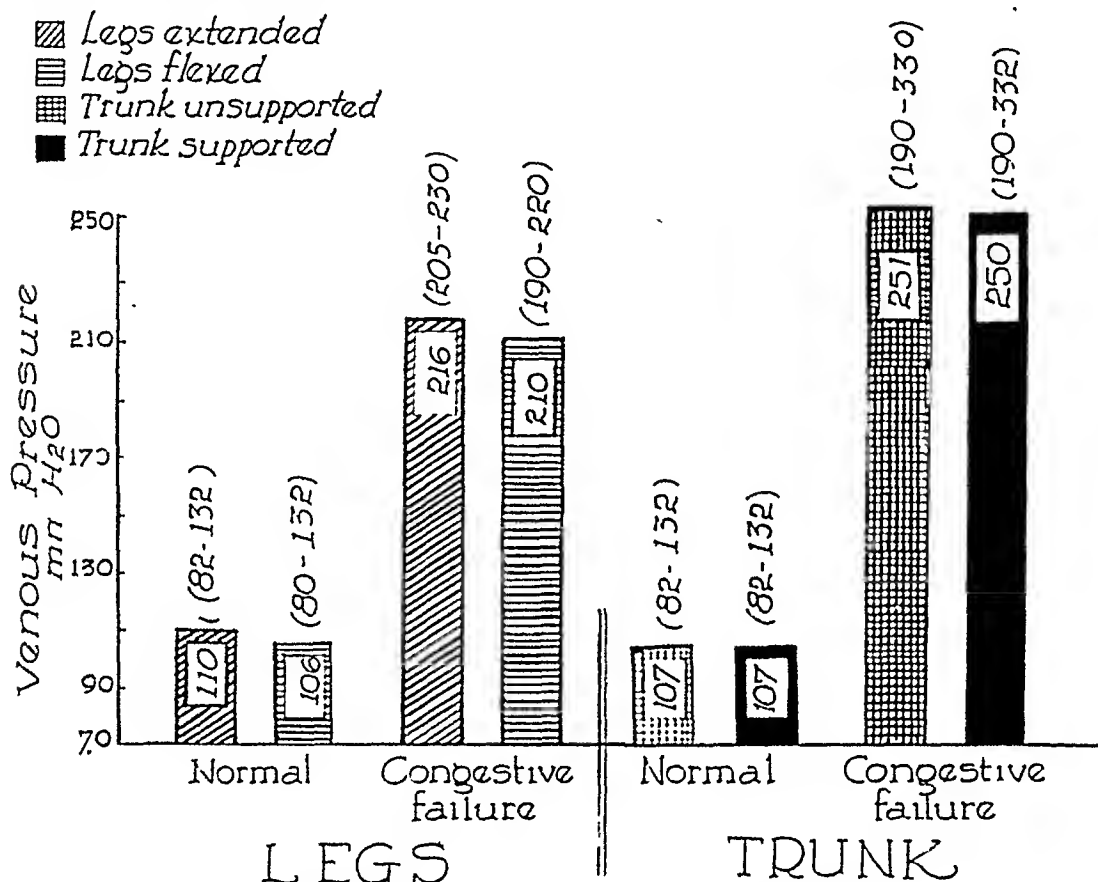


Fig. 7.—Venous pressures in 10 normal subjects and 10 patients with congestive heart failure, taken in the sitting position with the legs extended, then flexed, and with the trunk supported, then unsupported. Very few differences in pressures resulted.

Direction of Insertion of the Needle and Venous Pressure.—The venous pressure was measured in large and small veins with a 23-gauge needle, with the apex of the needle pointed first in the direction of and then against blood flow. The pressures in the median basilic vein at the antecubitus and in the greater saphenous vein at the ankle did not vary significantly with changes in needle direction. The average difference was 3 mm. of water (Fig. 6). The pressure in the small veins of the hands and feet was significantly higher (average, 15 mm. of water) when the needle was directed against the direction of blood flow. The greater differences in pressure in small veins are due to the great effects of the kinetics of flow, which are probably caused in large part by venospasm, as small veins are prone to contract tightly about the shaft of the needle and sometimes completely occlude the lumen of the vessel.

Position of the Legs and Trunk in Relation to the Venous Pressure in the Sitting Position.—Pressures in the median basilic vein were recorded in 10 normal subjects and 10 patients with right ventricular congestive heart failure (Fig. 7). Pressures were recorded with the subject sitting with the legs extended and with the legs flexed, the feet always being lightly supported. In both groups the pressures were slightly lower with the legs flexed. The pressure was then measured in the same individuals, sitting, with the trunk unsupported, then with the trunk supported by a backrest. The differences in venous pressures did not exceed 1 mm. of water under the latter conditions.

Respiration and Venous Pressure.—Certain statements can be made concerning the relationship between venous pressure and the phases of respiration. A 20-gauge needle was used to record the respiratory effects. The venous pressure fell slightly with normal quiet inspiration and rose with quiet expiration. Slow, deep inspiration greatly reduced the antecubital venous pressure, and slow deep expiration markedly increased it. The Valsalva experiment increased the pressure still more and the Müller experiment decreased it. Rapidly repeated deep inspirations caused a more marked fall in pressure than did one single deep inspiration. It is well to remember that the normal respiratory changes were often markedly altered in patients with venous hypertension (vide infra).

Muscle Tension and Venous Pressure.—Venous pressures were recorded in the veins of the arms and legs of ten subjects before and during muscle contraction. No difference in pressure was found in the median basilic vein. Tension of the muscles on the lower extremity sometimes resulted in a considerable increase in the pressures in the greater saphenous vein (average difference, 20 mm. of water). This increase may be due to obstruction of the deep veins of the legs, which places a greater load on the superficial veins in which the measurement is being made. It is possible that in unusually muscular individuals muscle tension in the arms may increase the pressure by the same mechanism.

ESTABLISHMENT OF NORMAL VALUES

Normal values for venous pressure were determined in 130 normal young adult male and female, Negro and white subjects. All measurements were made in either the supine or sitting position with the vein at the phlebostatic level.

Normal Values for the Median Basilic Vein of Adults in the Supine Position.—The pressures were recorded in the veins of the right and left arms of 70 subjects (Fig. 8). The pressures in the two arms did not differ, on an average, by more than 2 mm. of water in any group studied. The lowest pressures were encountered in the white females (average, 90.5 mm.; extremes, 80 to 116 mm. of water), and the highest pressures were encountered in the Negro males (average, 103.5 mm.; extremes 66 to 128 mm. of water). The average for both Negro and white females was 100.5 mm. of water. The highest value for the females was 128 mm. of water, and for the males 140 mm. of water. The average value for the entire group was 97 mm. of water, the range being 50 to 140 mm. of water.

Normal Venous Pressure Values for Various Veins of the Body in the Supine and Sitting Positions.—Venous pressures were recorded in various veins of the body in 100 subjects (Fig. 9). No significant difference between the pressures of the right and left sides of the body (arms or legs) was noted. The average pressures in the median basilic, femoral, and dorsal metacarpal veins,

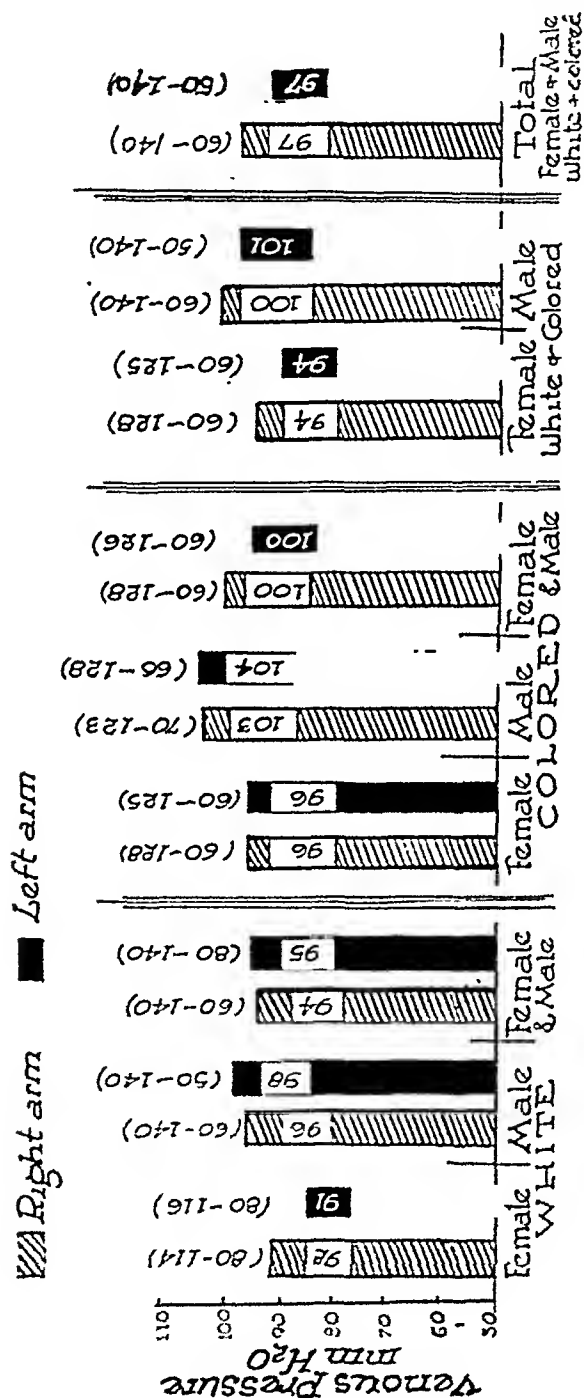


Fig. 8.—Venous pressures in the right and left arms in males and females and Negro and white subjects in the supine position. The average pressure for the group is 97 mm. of water, and the range is 50 to 140 mm. of water.

in the great saphenous vein at the ankle, and in the dorsal pedal veins were 97, 111, 120, 149.5, and 175.5 mm. of water, respectively. The ranges of pressure for these vessels were 50 to 140, 98 to 128, 70 to 146, 110 to 190, and 124 to

210 mm., respectively. Numerous venous pressure determinations in various veins in one subject are shown in Fig. 10.

The venous pressure in a dorsal metacarpal vein was compared with that in a median cubital vein in 20 sitting subjects (Fig. 11). There was an average difference of 26 mm. of water in the pressure of the veins of the elbow and hand in the sitting position, as compared with an average difference of 23 mm. of water in the pressure of these veins in the supine position. The pressures in the veins of the hands were always higher.

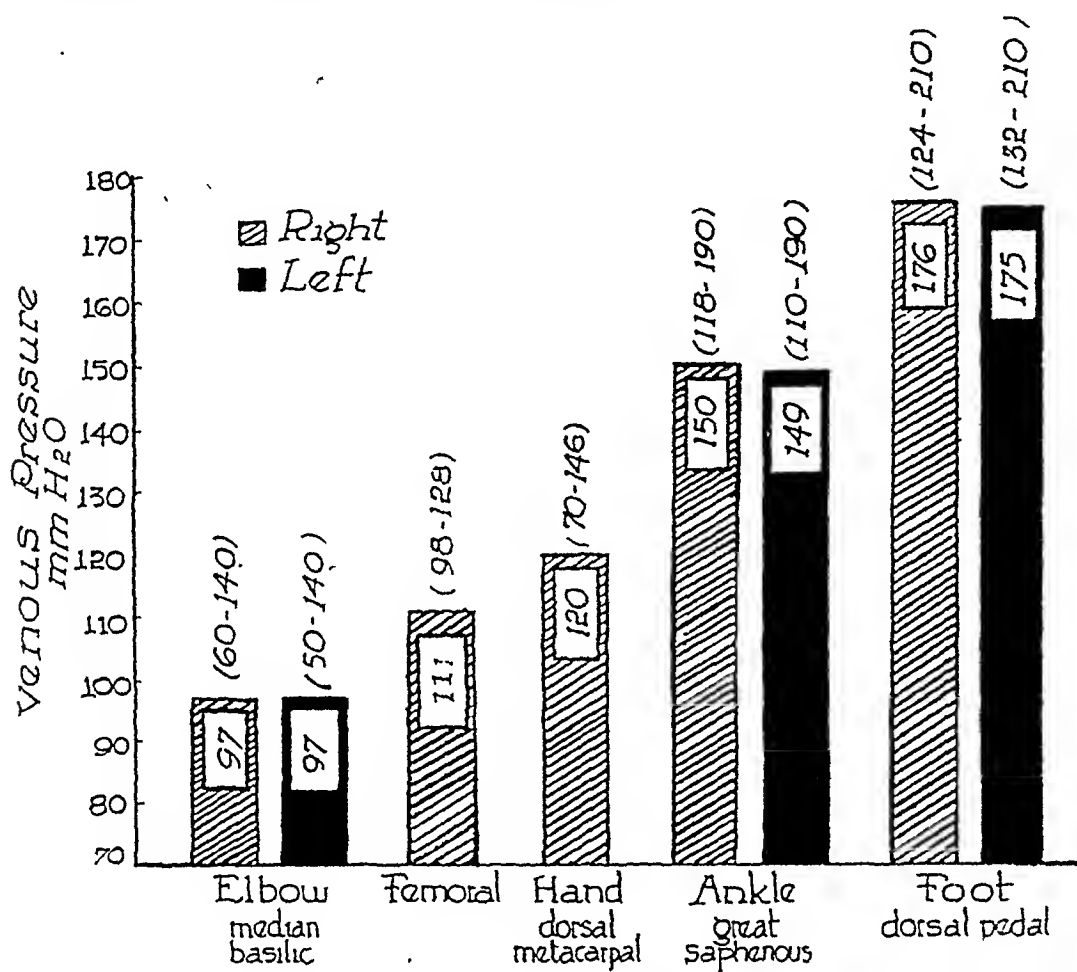


Fig. 9.—Venous pressures in 100 Negro and white subjects of both sexes. The pressures were taken in various veins of the body. In general, the greater the distance from the heart, the higher the venous pressure.

VENOUS PRESSURE IN PATIENTS WITH RIGHT VENTRICULAR CONGESTIVE HEART FAILURE

The following experiments illustrate some of the differences in venous pressure between normal subjects and 50 patients with cardiac disease with and without congestive heart failure.

Venous Pressure in the Supine and Sitting Positions.—The pressures in the median basilic veins in the supine and sitting positions were compared in 40 normal subjects and in 30 patients with Class I, Class III, or Class IV heart disease (Fig. 12). In the normal group the pressures in the supine and sitting positions showed no significant difference, being 3 mm. of water greater for the

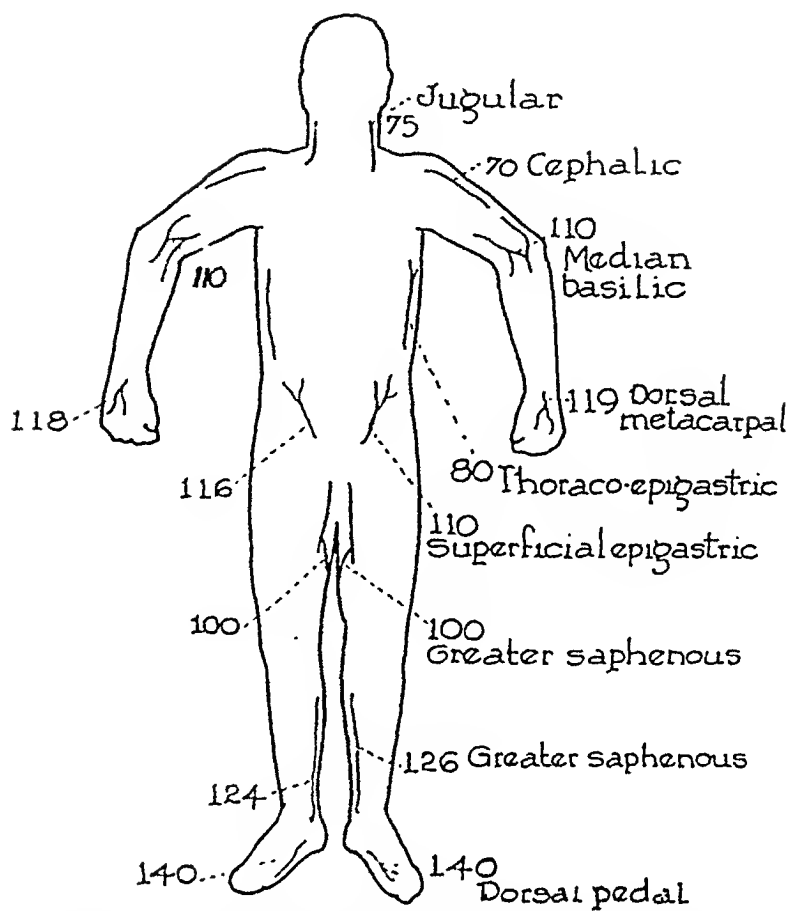


Fig. 10.—Venous pressures in various veins of one individual showing gradient of pressures from the periphery to the heart.

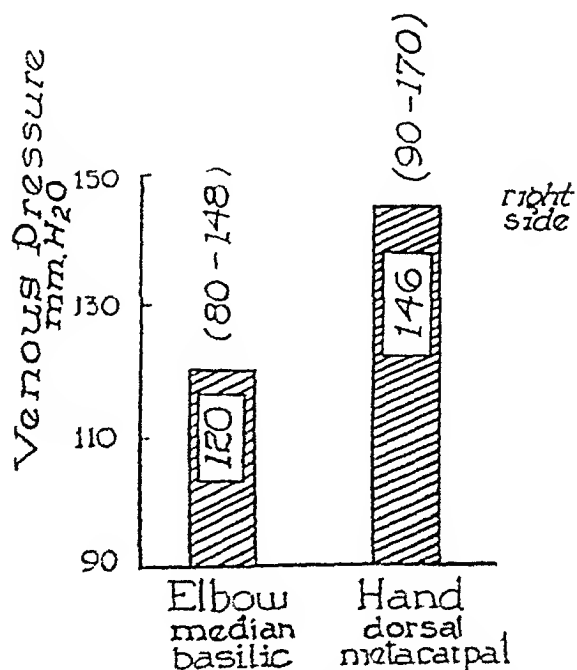


Fig. 11.—Venous pressures in the median cubital and dorsal metacarpal veins of 20 subjects in the sitting position. These values are not significantly different from the pressures in these veins with the subjects in the supine position.

supine position. In patients who were placed in Class I, that is, patients without clinical evidence of failure, the average pressure in the sitting position was 4 mm. of water less than that in the supine position. Patients with congestive heart failure who were placed in Class III or IV had venous pressures which were 76 mm. of water lower in the sitting than in the supine position. The

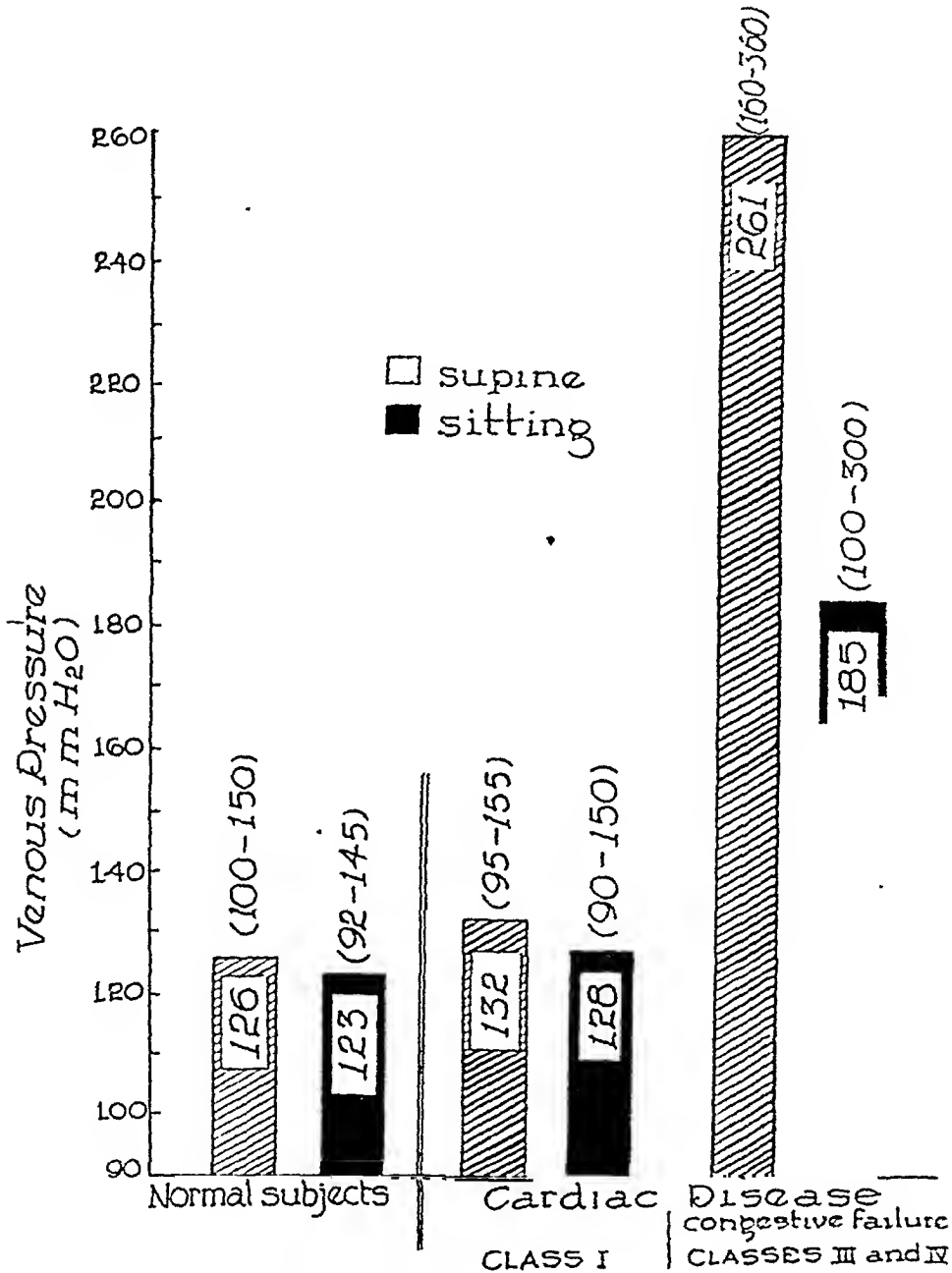


Fig. 12.—Venous pressures of 60 normal subjects and 50 patients with cardiac disease. These pressures were recorded in the median cubital vein, using the phlebostatic level for reference, with the subjects first in the supine position and then in the sitting position. The pressure recorded with the patient in the supine position was a better indication of the presence of congestive failure than was the pressure recorded with the patient in the sitting position.

average pressure in the supine position was 261 mm. of water, and in the sitting position 185 mm. of water. All the patients in Class IV had venous hypertension in the supine position, that is, a venous pressure greater than 140 mm. of water. However, 30 per cent of these patients had normal venous pressures in the sitting position.

Effect of Abdominal Compression on Venous Pressure.—The pressure in the antecubital vein was recorded in 40 normal supine subjects and 30 supine patients with varying degrees of cardiac disease with and without congestive heart failure (Fig. 13). Pressure was then manually applied over the umbilicus for a period of one minute.¹³ The region of the abdomen compressed

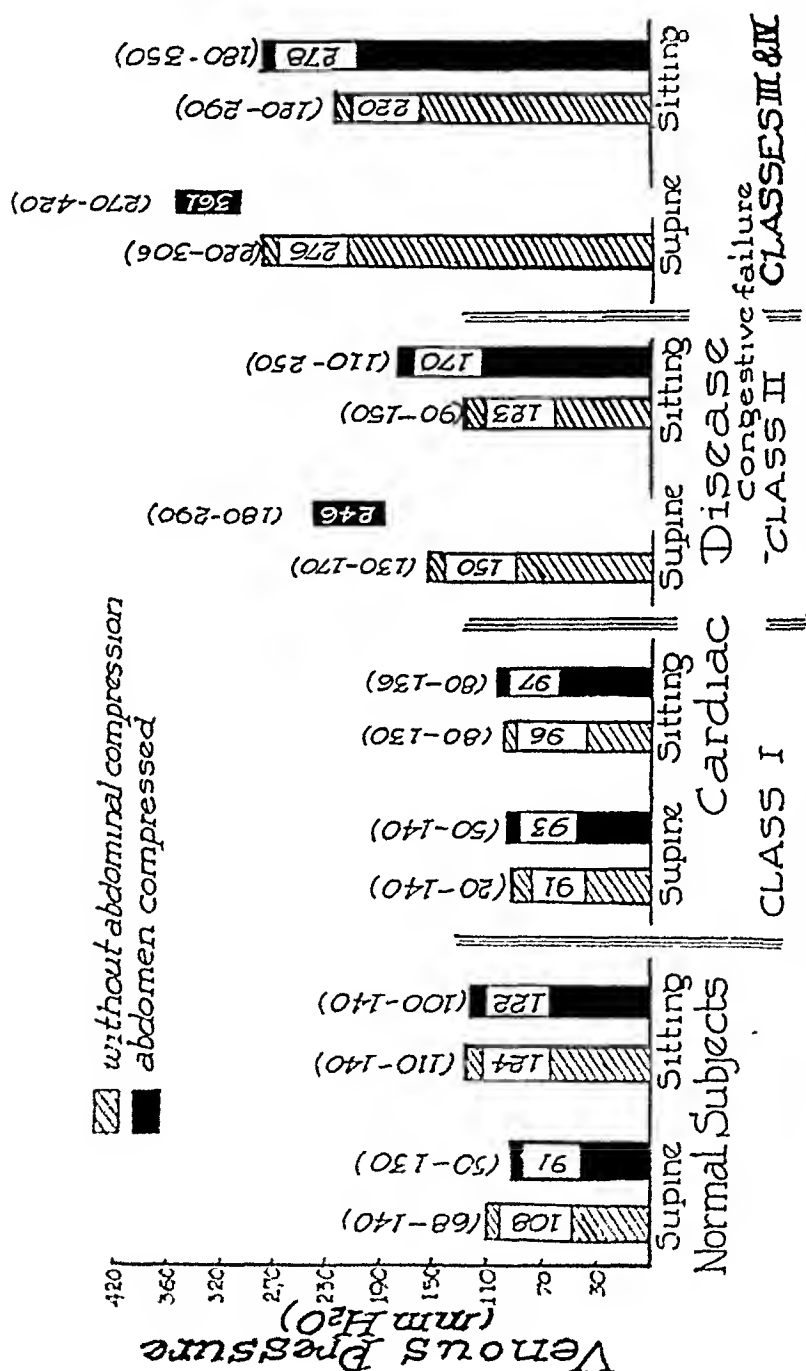


FIG. 13.—Effect of abdominal compression on the median cubital venous pressure of 30 normal subjects and 30 patients with cardiac disease in the supine and sitting positions.

was not important, since it was found that pressure exerted over the liver and over various other regions of the abdomen did not alter the results (*vide infra*). In all instances the patients were instructed to breathe naturally. Compression

of the abdomen of normal subjects resulted either in a fall in the venous pressure or in no change (Fig. 13). The average pressure before compression was 108 mm. of water; that during compression was 91 mm. of water, an average fall of 17 mm. of water. In the sitting position the average difference between the pressure before and that during compression was -2 mm. of water. In 30 per cent of these latter patients the pressure rose to + 10 mm. of water or less with abdominal compression.

In 10 patients with heart disease without failure (Class I) the results were essentially the same as for the normal subjects. The average pressure in the median basilic vein before abdominal compression, with the patient supine, was 91; during compression it was 93 mm. of water. Venous pressures before and during abdominal compression in the sitting positions were 96 and 97 mm. of water, respectively (Fig. 13).

In 10 patients with cardiac disease (Class II, mild congestive heart failure), the venous pressure in the supine position was only slightly greater than normal, averaging 150 mm. of water, and varying from 130 to 170 mm. of water. Abdominal compression produced a rise in pressure to an average of 246 mm. of water, an average increase of 96 mm. of water. Abdominal compression produced an average increase in pressure in these patients when sitting of 47 mm. of water (Fig. 13).

In cardiac patients resting in the supine position (Class III and IV, marked congestive heart failure), the average venous pressure before abdominal compression was 276 mm. of water and during compression 361 mm. of water, an average difference of 85 mm. of water. In the sitting position the pressure before abdominal compression was 220 mm. of water and that during compression was 278 mm. of water, an average difference of 58 mm. of water.

From these experiments it would seem that abdominal compression in supine patients with normal or borderline venous pressures is particularly useful in the diagnosis of early congestive heart failure.

Venous Normotension, Venous Hypertension, and Certain Clinical Findings in Patients With Congestive Heart Failure.—Clinical findings and venous pressures were recorded in 20 patients with heart disease, all of whom had clinical heart failure. From these data the following conclusions may be drawn: (1) Venous hypertension does not always exist even though other signs of right, left, or right and left ventricular congestive heart failure may be present. (2) Even though physical signs of right ventricular congestive failure are not striking, the venous pressure may be high if the pressure is recorded during rapidly progressing failure. (3) The venous pressure may be normal when other signs of right ventricular congestive failure are present, if the pressure is recorded during rapidly improving failure. Thus in some instances the venous pressures were within normal limits even in the presence of hepatomegaly, ascites, and edema of the legs. (4) When the antecubital venous pressure was 220 mm. of water or greater, the liver was always found to be enlarged. (5) When the pressure reached 250 mm. of water, ascites, leg edema, and orthopnea were always present.

DISCUSSION

The venous pressure in both healthy and diseased patients may be accurately determined by the Phlebomanometer, with an error not greater than ± 5 mm. of water. Careless determinations may result in gross inaccuracies. The most important sources of error were: (1) venous obstruction produced by kinking of veins, (2) breath-holding, (3) muscle contraction, (4) insufficient attention to the problem of heart level,¹⁴ (5) temporal variations, (6) spasm of veins, and (7) direction of insertion of the needle. To eliminate many of these sources of error the following procedure is advocated: Before a measurement is made, the subject should rest supine for ten minutes, with the arm placed at the phlebotatic level and abducted sufficiently to form an angle of approximately 60 degrees with the body. Clothing likely to produce venous obstruction should be loosened. Holbrook¹⁵ has shown that abduction of the arm to 90 degrees, as well as more marked abduction, produces abnormally high readings. Brandt and Katz¹⁶ found that abduction of the arm affects the anatomic relationship of the clavicle, first rib, and subclavian vein so as to exert pressure on the axillary and subclavian veins. The respirations should be watched to prevent sighing or breath-holding. Consecutive readings should be recorded until constant readings are obtained. It is desirable to make the measurement on a firm, flat table with the head of the subject on a low pillow. The use of a level and ruler may be employed for most accurate work but this is not necessary for most clinical purposes.

The choice of heart level is important in order to avoid great variations in results. A study of the literature showed great variation¹⁷⁻⁴⁰ in the points of reference and normal values for the antecubital vein obtained by direct methods for the supine position (Table I). The marked variations in normal values resulted chiefly from differences in the reference levels used as heart level. The normal range for the venous pressure with the phlebotatic level at the so-called heart level for the antecubital vein is 50 to 140 mm. of water. These values compare favorably with the normal values obtained by others using a constant heart level fixed 100 mm. from the table, as well as with measurements using the midaxillary line as the level of reference.^{2, 39, 40} It is desirable to have a level which cannot be used only for the supine position, but also for the upright sitting and intermediate sitting position. These and previous studies by the authors¹² indicate that a horizontal plane passing through an axis running between the lateral surfaces of the trunk half the distance from the anterior and posterior aspects of the body, at the level of the fourth intercostal space anteriorly, presents a suitable reference line or level from which to measure the venous pressure with the trunk in any of the afore-mentioned positions. Normally there is no significant difference in the venous pressure in the supine, intermediate sitting, or upright sitting position if the pressure is measured with the vein at the phlebotatic level. In the sitting position the trunk may be either supported or unsupported and the legs may be extended or flexed without significantly altering the antecubital venous pressure.

The applications of venous pressure determinations to clinical practice are numerous and are particularly useful in the diagnosis of right ventricular congestive heart failure, constrictive or effusive pericarditis, venous obstruction, and edema. In patients with congestive heart failure the venous pressure with the patient in the supine position was a much more reliable indication of failure than was the venous pressure taken in the sitting position. Abdominal compression was also a valuable aid in the diagnosis of congestive heart failure.¹³ The response to abdominal compression was abnormal in approximately 30 per cent of the patients whose antecubital venous pressure, taken when they were in the supine position, was normal or borderline. The compression procedures may be executed in the supine or sitting position. They are somewhat more sensitive in the former. The average rise in pressure of patients with Class II heart function (mild congestive failure) during compression was 96 mm. of water when supine and 47 mm. of water when sitting.^{41, 42} In the normal supine subject abdominal compression produced either a fall or no change in pressure in the median basilic vein (average was a fall of 17 mm. of water). In the sitting position, abdominal compression sometimes produced a rise in pressure of as much as 10 mm. of water (average was a fall of 2 mm. of water).

The mechanism of fall in venous pressure in the normal subjects is unknown. It is conjectured that abdominal compression interferes with venous return through the inferior vena cava. This results in a drop in venous pressure in the upper extremities and a rise in the lower extremities. In right ventricular congestive heart failure, abdominal compression probably forces blood from the already engorged venous reservoirs of the abdominal cavity into the thorax, which, in the presence of an inefficient heart, results in an increase in the pressure in the veins of the upper extremities. Similar results have been noted in the presence of pericarditis with marked effusion.¹³ Abdominal compression, when carried out in patients with ascites from causes other than heart failure produced no increase in the venous pressure in the antecubital vein.

When the antecubital venous pressure was recorded for the supine position and the arm was elevated 90 degrees, that is, perpendicular to the table, the pressure in normal patients fell markedly and approached atmospheric pressure. In the presence of marked congestive failure with an already elevated venous pressure, the pressure fell the same amount as in the normal subject, but remained considerably above atmospheric pressure. In normal subjects this phenomenon may be due to partial collapse of the vein, and in those with congestive failure to the inability of the overfilled vein to collapse. Abdominal compression, particularly when carried out in the supine position, reveals evidence of failure much earlier than does the finding of an elevated pressure after elevation of the arm.

In correlating the venous pressure with the clinical picture of failure it was noted that the pressure may be either high or normal in the presence of clinical signs of failure, depending upon whether the edema is increasing or decreasing. It would seem that an increase in venous pressure precedes the onset of the clinical manifestations of failure. When the pressure reached 250 mm. of water hepatomegaly, ascites, edema, and orthopnea were always present.

It must be remembered that these studies were conducted in patients who had had absolute bed rest, in a partially sitting position, with legs extended, for some days. These generalizations may not be entirely applicable to patients in other positions, such as the sitting position with legs down.

SUMMARY

A method of use of the Phlebomanometer was described. The phlebostatic level was defined as a horizontal plane passing through the phlebostatic axis which results from the intersection of a frontal plane passing half the distance from the base of the xiphoid to the dorsum of the body and a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. The use of the phlebostatic level as a level of reference gives comparable results in normal subjects in the supine, intermediate sitting, or upright sitting position.

Certain factors affecting the venous pressure were discussed. The pressure fell when the vein under study was raised above the phlebostatic level, and it increased as the vein was lowered below this level, the changes being equivalent to the hydrostatic effects. Venous pressures were higher in males than in females and in both sexes they were higher in the morning than in the evening. In one instance the morning-evening difference was 27 mm. of water. Venous pressures taken daily at a certain hour varied as much as 29 mm. of water. The venous pressure was higher immediately after inserting the needle into the vein, and fell to a constant level in four minutes. The venous pressure was ordinarily higher when the needle was inserted against the direction of blood flow than when it was inserted in the direction of flow. This difference was slight in the large veins, but was marked in the small ones, probably because of the greater effect of venous spasm in small veins.

Venous pressures taken in the median antecubital veins with the subjects in the sitting position were essentially the same with the trunk supported as with the trunk unsupported, and with the legs extended as with the legs flexed.

The pressure normally rose with expiration and fell with inspiration. The pressure was increased by the Valsalva experiment and decreased by the Müller experiment. Muscle tension of the legs increased the pressure in the greater saphenous vein at the ankle but did not increase the median antecubital pressure.

The average normal antecubital pressure in females (Negro and white) was 94 mm. of water, and in males (Negro and white), 100.5 mm. of water. The range of normal for both Negro and white males and females, in the median antecubital veins with the subject supine, was 50 to 140 mm. of water. Average normal pressures in the median basilic, femoral, and dorsal metacarpal veins, in the great saphenous vein at the angle, and in the dorsal pedal veins were 97, 111, 120, 150, and 178 mm. of water, respectively.

In patients with congestive failure the venous pressure taken in the supine position was a better index of failure than was the pressure in the sitting position, since the pressure with the patient supine was often elevated when the pressure with the patient sitting was normal.

In normal subjects resting in the supine position, compression of the abdomen ordinarily produced a fall in the antebrachial venous pressure, but usually produced a rise in this pressure when right ventricular congestive heart failure was present. Abdominal compression sometimes gave evidence of congestive failure when the venous pressure with the patient supine was within normal limits.

A correlation of the clinical signs and symptoms of congestive heart failure with the level of the venous pressure showed that, when the venous pressure was 250 mm. of water, ascites, leg edema, orthopnea, and hepatomegaly were always present in hospital bed patients with congestive failure.

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HEMODYNAMICS OF ACUTE HEMORRHAGE IN MAN

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THE adjustments of the circulation to acute hemorrhage have been extensively studied in experimental animals. A complete hemodynamic study of the effects of acute hemorrhage in man has been difficult because of the lack of a method for measuring the cardiac output and the right atrial pressure in acutely ill patients. The development of the technique of right atrial catheterization, as described by Cournand and Ranges,¹ made clinical studies of acute hemorrhage possible. The purpose of this paper is to describe the hemodynamics in thirteen patients with acute blood loss.

METHODS

The cardiac output was measured by the utilization of the Fick principle. An indwelling catheter in the right atrium, introduced by way of the antecubital vein, was used for measuring the pressure and obtaining samples of blood. A special needle was introduced into the femoral artery through which pressures were measured and blood samples were obtained. The mean right atrial pressure was measured with a manometer commonly used to measure venous pressures, the point of reference being 5 cm. posterior to the fourth costochondral junction.

Blood samples for oxygen analyses were collected under oil and analyzed by the method of Van Slyke.² The oxygen consumption was determined by the analysis of a two- or three-minute sample of expired air, using the method of Haldane. The femoral arterial pressure was recorded optically by the method of Hamilton.³ The mean arterial pressure was measured by planimetric integration of the area beneath the tracing. The peripheral resistance was calculated by the formula:

$$R = \frac{P_m \text{ (mean pressure in mm. Hg)} \times 1332}{C.O. \text{ (cardiac output in ml. per sec.)}^4$$

Hemoglobin concentration was measured with a photoelectric colorimeter. Heparin was used as the anticoagulant to determine the hematocrit reading. The plasma volume was measured by the injection of the dye T 1824. Concentra-

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tions in serial blood samples were determined with a Beckmann spectrophotometer. Blood alcohol concentrations were determined by the method of Harger⁵ whenever there was any clinical evidence of alcoholism.

RESULTS

Observations were made on 13 patients with acute blood loss (Table I). In 11 patients hemorrhage was the result of knife wounds. These patients were brought immediately to the hospital and studies were usually begun within an hour. The other two patients had bleeding into the gastrointestinal tract from a peptic ulcer. In none did the circulation appear normal. The systolic arterial pressure was below 100 mm. Hg in each instance. The hemorrhage was acute in the majority of the patients, and complete hemodilution had not occurred. In nine patients the hemoglobin level was 10 Gm. or more per 100 c.c.; in four the level was between 9 and 10 Gm. The plasma volume was measured in seven patients and was found to be below the expected normal level in each instance.

The cardiac output values are difficult to compare with those of control subjects because the cardiac output normally varies with the size of the subject. For this reason we will compare the cardiac index (output in liters per minute per square meter of body surface) of patients with hemorrhage with the cardiac index of normal subjects.

The cardiac index of normal young males in the basal state in our laboratory averaged 3.3, with a range of 2.3 to 4.1.⁶ The patients with hemorrhage were brought in from the street, usually in the evening, and were not basal. Many of them were restless and in five subjects the situation was complicated by acute alcoholism. Had it not been for the blood loss, the average cardiac index in this group would certainly have exceeded that of our basal subjects. We have assumed that cardiac output was inadequate in all patients in whom the cardiac index was below 2.6 and that it was probably inadequate when the index was below 3.

In the five patients with the cardiac index ranging from 2.7 to 5, the clinical signs and symptoms of mild shock were present. The atrial pressure tended to be low and the mean arterial pressure was decreased. The average arteriovenous oxygen difference was 4.2 volumes per cent (normal, 4), and the average cardiac index was 3.5 (normal, 3.3). The peripheral resistance tended to be low.

The cardiac index was below 2.6 in eight patients. These patients presented the typical clinical picture of circulatory failure. The oxygen consumption was not decreased. The arteriovenous oxygen difference was considerably increased. The systolic, diastolic, and mean arterial pressures were greatly lowered. The atrial pressures were low, but not significantly lower than in the group with a higher cardiac index. The peripheral resistance was never decreased. The average was 1,560, as compared with 1,160 in the control group. The peripheral resistance was not related to the level of the blood alcohol. The heart rate varied from 68 to 107 beats per minute. There was no correlation between the degree of reduction in cardiac output and the heart rate.

Restoration of the blood volume with physiologic salt solution, human albumin solution, whole blood, or gelatin solution resulted in an increase in cardiac output, atrial pressure, and arterial pressure. The peripheral resistance usually fell sharply. The heart rate either decreased, increased, or showed no change.

DISCUSSION

The sequence of events which occur when blood is removed from the body can now be described in more detail as the result of the data reported in this paper and in other recent contributions to the literature.

The removal of from 400 to 900 c.c. of blood causes a fall in atrial pressure without any other significant finding except a slight rise in heart rate.⁷ The same results are obtained when blood is pooled in the extremities by venous tourniquets.⁷ The results obtained by the catheter technique have been confirmed in our laboratory by the ballistocardiograph and support the conclusions drawn from the ballistocardiographic studies reported by Starr and his co-workers.⁸ They are at variance with the results of McMichael and Sharpey-Schafer,⁹ who measured the cardiac output by the catheter technique after venisection and found an almost linear relationship between the fall in atrial pressure and the decrease in cardiac output.

The patients reported here had lost sufficient blood to cause circulatory insufficiency and represent a more advanced stage of blood loss than had been produced in this laboratory by the removal of blood from volunteer donors.⁷ The atrial pressure was found to be lower than that in the control group, but not lower than that in the donors who had been bled or in the normal subjects who had blood pooled in their extremities from the application of venous tourniquets.⁷

The fact that no further lowering of the atrial pressure was found in these subjects with severe circulatory failure is of interest. That the circulatory deficiency was the result of a decrease in blood volume was amply demonstrated by the results of therapy. Increasing the blood volume uniformly increased the cardiac output. It may be that the relationship between the blood volume and atrial pressure is not linear. Under these circumstances the removal of the first few hundred cubic centimeters of blood would cause a greater and more obvious fall in atrial pressure than would the subsequent removal of equal amounts. The mean atrial pressure as measured with a water manometer may not reflect the actual variations in atrial pressure throughout the heart cycle. Changes in pleural pressure may have masked a decrease in effective atrial pressure. The problem needs further investigation.

Patients who are injured may have reflex vasodilatation with the picture of acute circulatory collapse. In this condition the peripheral resistance falls to a low level without a corresponding fall in cardiac output or atrial pressure.¹⁰ Reflex vasodilatation may well have accounted for a lowering of the arterial pressure in certain patients reported in this paper. In all of the patients with a cardiac index below 2.6 the peripheral resistance was normal or high, indicating that reflex vasodilatation had played no part in the low arterial pressure. The

findings are similar to those reported in dogs and indicate at least normal arteriolar constriction in this stage of hemorrhagic shock.¹¹

In these patients hemodilution was not completed at the time the observations on the circulation were made. When anemia becomes more marked the picture is somewhat more complicated because the heart must pump more of the anemic blood to supply the body needs.¹² During the acute stage of blood loss the circulation becomes steadily smaller. As hemodilution occurs and anemia develops the cardiac output will rise to the normal level. If the hemodilution continues the anemia will stimulate the heart to pump more blood and the circulation will become hyperactive. This sequence of events may be seen in a short period of time if plasma or albumin is given and immediate hemodilution accomplished.

CONCLUSIONS

1. Studies of the hemodynamics were made in 13 patients with circulatory insufficiency resulting from acute blood loss. Right atrial catheterization was employed to secure mixed samples of venous blood and measure the mean right atrial pressure. The cardiac output was calculated utilizing the Fick principle. The femoral arterial pressure was recorded optically.

2. In all of the patients the femoral arterial pressure was below 100 mm. of mercury. Complete hemodilution had not occurred and the blood volume was decreased at the time of the study.

3. In the five patients with cardiac index above 2.6, signs and symptoms of mild shock were present. The arterial and atrial pressures were decreased, but the cardiac output, arteriovenous oxygen difference, and the peripheral resistance were within the normal or low normal range. Reflex arteriolar dilatation may well have accounted in part for the low arterial pressure.

4. In the eight patients with cardiac index below 2.6, the circulation was definitely abnormal. The arteriovenous oxygen difference was increased, the atrial and arterial pressures were low. The peripheral resistance of the group as a whole was elevated.

5. An increase in blood volume by the use of intravenous fluid always caused a rise in atrial and arterial pressures, an increase in cardiac output, and a fall in peripheral resistance.

6. Circulatory failure from hemorrhage may be complicated by reflex vasodilatation as occurs in the common faint. If it is uncomplicated by this factor, it is not associated with arteriolar dilatation during the first few hours.

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THE CIRCULATION IN PENETRATING WOUNDS OF THE CHEST:
A STUDY BY THE METHOD OF RIGHT HEART
CATHETERIZATION

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PENETRATING wounds of the chest are frequently associated with profound circulatory disturbances. On admission to the hospital patients with such chest wounds present a striking clinical picture characterized by restlessness, sweating, cold extremities, and weak, thready pulse. They appear so acutely ill that the administration of fluid by vein is usually begun immediately. In all cases, the condition is complicated by some degree of hemorrhage, either external or into the pleural space. The majority of these patients improve in a short time and characteristically have no further circulatory difficulty unless they continue to bleed internally. It was impossible to decide on clinical grounds whether the circulatory collapse was the result of blood loss alone or the result of some other mechanism related to the wound in the pleura and lung.

In order to understand more clearly the state of the circulation in these patients, quantitative hemodynamic data were collected on thirteen patients with penetrating wounds of the pleura.

• METHODS

The techniques used in this study have been described elsewhere.^{1,2} The right atrium was catheterized to obtain samples of mixed venous blood and to measure the right atrial pressure. The arterial pressure was recorded optically from a needle placed in the femoral artery.

The cardiac output is recorded as the cardiac index which is the output of the heart per minute per square meter of body surface. The use of the cardiac index facilitates the comparison of data between subjects of different height and weight.

RESULTS

Thirteen patients with chest injuries were studied (Table I). Ten patients received their injuries from knives, two from bullets, and one as a result of multiple fractured ribs. Eleven of these had blood within the pleural cavity, one had a fairly large extrapleural hematoma, and one had free air in the mediastinum but no evidence of extravasated blood in the chest. In only two cases

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PATIENT	DIAGNOSIS	AGE	SEX	SURFACE AREA	OXYGEN CONSUMPTION		VENTILATION		ARTERIAL OXYGEN CONTENT	MIXED VENOUS OXYGEN CONTENT	ARTERIOVENOUS OXY-GEN DIFFERENCE	CARDIAC INDEX		HEMOGLOBIN	HEMATOCRIT READING	FEMORAL ARTERIAL PRESSURE			PULSE RATE	PERIPHERAL RESISTANCE	ATRIAL PRESSURE	BLOOD VOLUME	OXYGEN SATURATION OF ARTERIAL BLOOD	MG. PER 100 C.C.
					C.C. PER MIN. PER SQ. M.	L. PER MIN. PER SQ. M.	L. PER MIN. PER SQ. M.	VOLUME PER CENT				SYSTOLIC	DIASTOLIC			MEAN								
J. J. McM.	Hemothorax, transection of cord, bullet wound	23	M	2.01	160	4.3	4.3	15.7	9.5	6.2	2.5	12.7	43	36	26	32	100	490	65			89	88	
W. W.	Hemothorax, stab wound	33	M	1.83	192	4.7	4.7	16.2	10.6	5.6	3.4	14.9	43	63	45	51	75	650	45		3,170		52	
W. L. T.	Extrapleural wound	52	M	1.87	107½	3.5	3.5	13.6	9.4	4.2	2.6	10.0	32	71	42	50	75	830	25		2,060		290	
P. D.	Hemothorax, stab wound	31	M	1.67	151	3.3	3.3	15.0	10.1	4.9	3.3	8.2	27	80	48	62	65	1,030	5		1,780		155	
O. M.	Hemothorax, stab wound	20	F	1.46	122	3.8	3.8	9.4	5.7	3.7	4.4	12.5	42	88	56	66	88	730	20		2,360		121	
L. D.	Hemothorax, stab wound	27	M	1.65	167	3.8	3.8	14.7	10.9	3.8	3.3	10.0	31	92	53	69	125	920	25			92	90	
T. L.	Hemothorax, bullet wound	28	F	1.83	160	3.8	3.8	12.2	7.3	4.9	4.0	11.9	37	94	59	68	92	840	35					
J. B. R.	Hemothorax, stab wound	42	M	1.61	158	3.3	3.3	15.2	11.3	3.9	3.1	13.5	39.5	77	46	54	77	850	65		2,980	88		
A. E.*	Hemothorax, fractured ribs	71	F	1.57	104	6.4	6.4	8.2	2.6	5.6	1.8	8.6	29	105	45	54	103	1,250	70		1,710	67		
D. S.	Hemothorax, stab wound	35	F	1.69	130	2.8	2.8	14.4	10.9	3.5	3.8	9.6	38	103	67	83	111	738	85		2,030			
R. G.	Hemothorax, stab wound	44	M	2.0	149	4.9	4.9	15.5	11.7	3.8	3.9	13.3	40	119	77	93	94	940	100					
J. J. T. C.	Hemothorax, stab wound	31	M	1.6	207	4.8	4.8	16.6	11.9	4.6	4.5	13.7	44	139	80	103	94	1,140	40			91	63	
M. M.	Mediastinal emphysema, stab wound	40	M	1.74	189	4.5	4.5	10.7	7.1	3.6	3.0	13.6	42	154	86	104	125	1,320	0				95	
Averages of the four patients without clinical evidence of circulatory insufficiency					169	4.2	4.2		3.9		4.3		41	129	78	96	106	1,040	56					
Averages of the eight patients with clinical evidence of circulatory insufficiency					152	3.8	3.8		4.7		3.3		37	75	47	57	87	790	36		2,600			
Averages of 13 patients with acute hemorrhage†					128	4.0	4.0		5.5		2.6		33	86	54	65	96	1,330	2		2,100			
Average normal values‡					128	3.1	3.1		4.0		3.3		124	67	85	68	1,160	31						

*Not included in averages. †Reference 1. ‡Reference 2. †Air sample taken after albumin was given. ‡The blood alcohol determination was not made if there was no clinical evidence of alcoholism.

was there evidence of free air in the pleural cavity, and this was only slight. Only one patient (A. E.) was cyanotic.

Four of the patients with penetrating pleural wounds showed no clinical evidence of circulatory insufficiency on admission to the hospital. The data on the circulation in these patients were similar to those obtained in apprehensive normal subjects.² The cardiac output was somewhat elevated and the heart rate was increased. The atrial pressure was unaltered.

In nine patients clinical evidence of circulatory insufficiency was present. Eight of these patients were observed shortly after injury. One of them, J. McM., had, as a complication, a transverse section of the dorsal cord. The ninth was a 71-year-old woman (A. E.), who had fractured several ribs and the tibia twelve hours before admission. Because none of our normal subjects were elderly, the data of patient A. E. were not averaged with those of the other eight patients with circulatory insufficiency from chest wounds. In each of the other eight patients with clinical signs of circulatory insufficiency the systolic arterial pressure was below 100 mm. Hg; in five it was 80 mm. or lower. In general, the pulse rate was not greatly elevated. In three it was 75 beats per minute or lower. The atrial pressure was not significantly different from that found in normal subjects.

The cardiac output was surprisingly high in these eight patients with signs of circulatory insufficiency. The marked fall in arterial pressure without a corresponding fall in cardiac output indicated a decrease in peripheral resistance. This could not be correlated with the level of the blood alcohol. In only three instances was the cardiac index below the average normal value of 3.3, and even in these patients it was not below the lower range of normal values.² In general the values were similar to those found in normal subjects in the basal state. As these patients were not basal and were generally in some pain it may be argued that the finding of a cardiac index comparable to that present in the normal basal state indicated some degree of circulatory insufficiency. The fact that the arteriovenous oxygen difference was only slightly increased above normal argues against any considerable degree of disproportion between the requirements of the body for blood and the cardiac output.

The oxygen consumption tended to be somewhat elevated. The plasma volume was measured in five of the eight subjects and found to be diminished from hemorrhage in three of them. The average ventilation in the eight patients with circulatory insufficiency was found to be 3.8 liters per minute per square meter. In the four patients who were not in circulatory difficulty the average ventilation was 4.2 liters per minute per square meter. This compares with a value of 3.4 for normal subjects and 4.2 for patients with moderate chronic anemia.³

Five patients received 50 Gm. of human albumin* intravenously. The arterial pressure rose during the therapy. The average increase in cardiac index was 0.9.⁴ The therapy may or may not have caused improvement. Spon-

*The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

taneous recovery may have occurred. Five patients with hemorrhage from superficial lacerations were treated with albumin and the average rise in cardiac index was 1.8.⁴

DISCUSSION

The clinical picture of these patients with penetrating wounds of the pleura is similar to that presented by patients with acute blood loss from multiple lacerations. The hemodynamic data, however, differ in several important ways in the two groups. Patients with simple acute blood loss and a systolic arterial pressure below 100 mm. Hg usually have a diminished cardiac output, a low atrial pressure and an elevated peripheral resistance. When the blood volume is increased by therapy, the rise in cardiac output is marked. In the patients reported here with knife wounds of the pleura, the cardiac output was relatively normal in spite of the sharp fall in arterial pressure and did not increase markedly when the blood volume was raised. The atrial pressure was not decreased and the peripheral resistance was lowered. It seems therefore that the sequence of events leading to the fall in arterial pressure is not the same in patients with chest wounds as in patients with blood loss alone.

The sudden circulatory collapse which occurs in donors while blood is being removed has been studied in this⁵ and other laboratories.^{6, 7} The subjects become pale, sweat profusely, and complain of nausea and weakness. The heart rate slows, the atrial pressure remains unchanged or increases, and the cardiac output remains unchanged. There is a striking fall in arterial pressure and peripheral resistance. The circulatory collapse appears to be the result of a sudden decrease in peripheral resistance because of vasodilatation, presumably in the arterioles. As this type of circulatory collapse does not result from a marked fall in atrial pressure and as it may occur before any blood is actually withdrawn, the fall in arterial pressure and peripheral resistance is believed to result from reflex dilatation of the arterioles. The skin vessels are contracted as shown by the marked pallor, but the vessels in the muscles are dilated.⁶ It is not unusual for the vessels supplying the skin and muscles to react in an opposite way to the same stimulus.⁶ The afferent impulse initiating the vasodepressor reflex may come from any of the special sense organs or any sensory nerves.

The changes in the circulation noted in these patients with circulatory collapse from chest wounds are similar to the changes found in subjects with acute reflex arteriolar dilatation. The afferent impulses for the vasodepressor reflex may well originate in the pleura. It has been shown in dogs that irritation of the pleura will result in a striking fall in arterial pressure.⁹ In the patients reported here extensive trauma to the chest wall was not present and all of the wounds were easily closed. The findings in patients with crushing wounds of the thorax and with extensive destruction of the chest may differ from those in our patients.

SUMMARY AND CONCLUSIONS

1. Quantitative hemodynamic data on 13 patients with chest injuries are presented. Four of these patients had no evidence of circulatory difficulties

while nine of them did. The studies on those without circulatory difficulty gave values which were similar to those on normal subjects previously reported from this laboratory.

2. The nine patients who had circulatory insufficiency showed hypotension, a low peripheral resistance, a relatively normal cardiac output, and a normal right atrial pressure. A group of patients who had circulatory insufficiency following acute hemorrhage showed hypotension, an increased peripheral resistance, a low cardiac output, and a low right atrial pressure.

3. The circulatory failure in these patients with penetrating wounds of the pleura appeared to be primarily the result of arteriolar dilatation. It is believed that the arteriolar dilatation is reflex in origin and it is suggested that the afferent impulses may arise in the pleura.

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PERICARDIAL TAMPONADE FROM STAB WOUND OF THE HEART AND PERICARDIAL EFFUSION OR EMPYEMA: A STUDY UTILIZING THE METHOD OF RIGHT HEART CATHETERIZATION

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PATIENTS with penetrating wounds of the heart with pericardial tamponade often present the clinical picture of profound shock. Study of these patients demonstrates the presence of a significantly different hemodynamic situation from that occurring in patients with shock produced by hemorrhage or by stab wounds of the chest. Observations on the changes in the circulation in seven patients with pericardial tamponade from stab wounds of the heart or from infection of the pericardium form the basis for this report.

METHODS

The methods used in this study have been described previously.^{1,2} The technique of right atrial catheterization was utilized for obtaining samples of mixed venous blood and for measuring the atrial pressure. The cardiac output was calculated utilizing the Fick principle. The arterial pressure was recorded optically from a needle placed in the femoral artery.

A comparison of the output of the heart per minute between subjects of different size is of little value. The heart of a large person normally pumps more blood than that of a small person. For this reason the cardiac index which is the output of the heart per minute per square meter of body surface is used in comparing the observations on patients with pericardial tamponade with those made on other groups.

RESULTS

Four patients with stab wounds over the precordium were studied soon after injury. Three of the four had a low arterial pressure and were sweating profusely on admission. S. W. was in shock when the first observations were obtained. R. B. received 1,000 c.c. of physiologic saline solution and 500 c.c. of blood in the emergency clinic and showed no sign of shock by the time the catheter was passed. W. S. was pulseless on admission but had improved without treatment before studies were made. All had evidence of increased venous pressure on inspection of the neck veins. On fluoroscopy the excursions of the heart borders were either not visible or greatly diminished. In one (S. W.), pericardial tamponade was proved at operation. In the other three the location

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of the stab wound, the decreased pulsations of the borders of the heart, the increased atrial pressure, and the paradoxical pulse made the clinical diagnosis fairly definite.

The cardiac output was definitely decreased in S. W. and probably decreased in W. S. These patients were not basal, were somewhat apprehensive, and would have been expected to have had a cardiac index at least as high as the average normal value (3.3) found in basal subjects.²

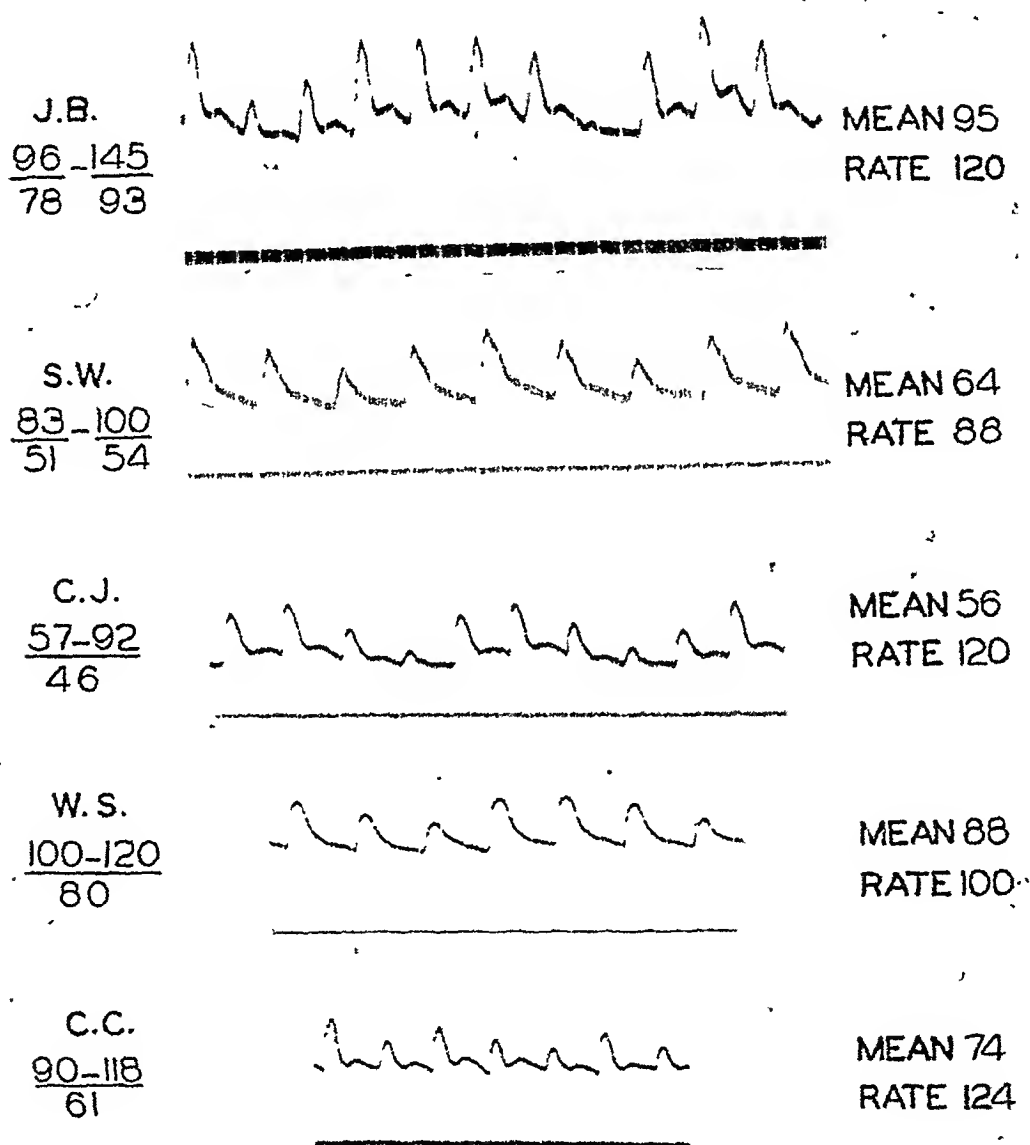


Fig. 1.—Femoral arterial pressure tracings showing paradoxical pulse of patients with pericardial tamponade, two as result of hemopericardium from stab wounds and three as result of pericardial infection.

The atrial pressure was greatly elevated in all the patients. There was no correlation between the height of the atrial pressure and the cardiac output. The arterial pulse was paradoxical (Fig. 1) in every instance. The systolic pressure fell 16 to 20 mm. Hg even during quiet inspiration. The peripheral resistance was in the high normal range in the two instances in which the cardiac output was decreased. The pulse rate ranged from 76 to 100 beats per minute and was 88 in the patient with the lowest cardiac index.

TABLE I. HEMODYNAMIC DATA OF SEVEN PATIENTS WITH PERICARDIAL TAMPONADE

PATIENT	DIAGNOSIS	AGE YRS.	SEX	SURFACE AREA SQ. M.	ORAL TEMPERATURE ° F.	OXYGEN CONSUMPTION		ARTERIAL OXYGEN CONTENT	MIXED VENOUS OXYGEN CONTENT	ARTERIOVENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT		CARDIAC INDEX		HEMOGLOBIN GM. PER 100 C.C.	HEMATOCRIT PER CENT	RESPIRATION VARIATION IN SYSTOLIC BLOOD PRESSURE		MEAN PULSE RATE	ATRIAL PRESSURE MM. H ₂ O	PERIPHERAL RESISTANCE ABSO- LUTE UNITS	MG. PER 100 C.C.
						C.C. PER MIN. PER SQ. M.	VOLUMES PER CENT				L. PER MIN.	L. PER MIN. SQ. M.	L. PER MIN. SQ. M.	MM. OF Hg PER MIN.			MM. OF Hg PER MIN.					
S. W.	Stabbed heart After 50 Gm. of albumin intravenously	32	M	1.8		111 109	16.2 14.1	10.4 9.4	5.8 4.7	3.4 4.2	1.9 2.3	15.4	45	17 12	64 73	88 84	160 255	1,500 1,390			230	
W. S.	Stabbed heart 17 days later	19	M	1.86		139 161	13.9 15.1	7.7 10.7	6.2 4.4	4.2 6.8	2.3 3.7	12.7 12.5	41	20 0	88 112	100 65	180 60	1,680 1,320			147	
N. B.	Stabbed heart After 500 c.c. 5% albu- min	39	M	1.72		180 173	12.8 11.7	7.0 6.9	5.8 4.8	5.4 6.6	3.2 3.8	11.0 10.7	34	16 12	72 77	88 88	135 190	1,070 930			360	
R. B.*	Stabbed heart 4 days later	42	M	1.76		199 143	14.3 16.5	9.1 12.2	5.2 4.3	7.0 5.9	4.0 3.4	13.0 13.5	40	17 5	89 102	76 97	240 - 5	1,020 1,380				
C. J.	Amoebic pericarditis 7 minutes after with- drawing 750 c.c. of fluid	17	M	1.55	97.4	127 155	10.4 10.6	2.0 6.1	8.4 4.5	2.3 5.3	1.5 3.4	8.3 8.5	28.4 28.8	35 12	56 79	120 104	300 180	1,960 1,200				
C. C.	Anaerobic streptococcus pericarditis 15 minutes after withdrawing 410 c.c. of fluid		M	1.82	102.4	275 243	15.8 12.7	7.8 8.5	8.0 4.2	6.3 10.5	3.5 5.8	13.8 13.4	41 43	28 14	74 92	124 112	195 125	940 700				
J. B.	Tuberculous pericarditis After withdrawing 1,100 c.c. of fluid	62	M	1.90	100.4	166 178	12.3 12.8	5.7 7.9	6.6 4.9	5.0 6.9	2.6 3.6	10.1 10.1	33 31	49 23	95 92	120 124	190 90	1,530 1,070				

*Five hundred cubic centimeters of blood and 1,000 c.c. of physiologic saline were given prior to control studies.

Two patients were given fluid intravenously after the initial observations had been made. N. B. received 25 Gm. of albumin* in 500 c.c. of physiologic saline solution, and S. W. received 50 Gm. of albumin in 200 c.c. of fluid. The atrial pressure rose 55 and 95 mm. of water, respectively. In each instance the arteriovenous oxygen difference decreased, the cardiac output rose, the mean arterial pressure increased, and the femoral pulse became somewhat less paradoxical. The evidence of an improved circulation was not striking but because the changes in blood pressure, arteriovenous oxygen difference, and cardiac output all went in the same direction, it was believed that the therapy with albumin was beneficial.

Three patients with pericardial tamponade as a result of infection of the pericardium were studied. All had distended neck veins and paradoxical pulse, but only one of these had marked clinical evidence of shock.

The cardiac output was inadequate for the needs of the body in each instance, as shown by the elevated arteriovenous oxygen difference before therapy and by the sharp rise in output as the tamponade was relieved. In two patients the absolute values for the cardiac index were low and the values for the peripheral resistance were in the high normal range. In all three of the patients a rise in output and a fall in peripheral resistance occurred as the pericardial fluid was removed. The arterial pulse was markedly paradoxical in each instance falling from 28 to 49 mm. Hg during quiet inspiration. The atrial pressure varied from 190 to 300 mm. of water (average normal value, 31 mm. of water).² The pulse rate was uniformly elevated.

The pericardial sac was tapped and from 410 to 1,100 c.c. of fluid were removed. The arteriovenous oxygen difference decreased, the cardiac output increased, the pulse became less paradoxical, and the peripheral resistance decreased. The fall in atrial pressure ranged from 70 to 120 mm. of water. The condition of the patients was improved greatly.

DISCUSSION

The clinical picture of pericardial tamponade has been well described. Its occurrence from a stab wound of the heart is not uncommon at Grady Hospital.³ On admission the patient is confused, pulseless, and frequently incontinent of urine and feces. The veins of the neck are distended, and the pulse if palpable is paradoxical. The patient may remain in this condition, he may spontaneously improve, or he may improve while fluids are being administered intravenously. The pulsations of the cardiac borders are either diminished or absent. This finding and the increased venous pressure persist even if the circulation improves.

When the patient is first seen it is difficult to be certain whether circulatory failure is the result of reflex arteriolar dilatation as frequently occurs in stab wounds of the chest⁴ or whether it is the result of pericardial tamponade. In certain patients with prompt improvement of the circulation without therapy,

*The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

reflex vasodilatation is the most likely primary cause of the shock picture. In others the persistence of the circulatory failure until the pressure within the pericardial sac is lowered is proof that the tamponade is the primary cause of the circulatory failure. External hemorrhage can be excluded as the primary factor because of the increased atrial pressure, but even then blood loss may be a contributory factor. Increased atrial pressure and paradoxical pulse are the first signs of circulatory failure produced by the rise of pressure within the pericardial sac. The pulse may become distinctly paradoxical before there is a detectable reduction in the minute output of the heart.

It is of interest to note that the atrial pressure in the two patients with decreased cardiac output did not rise over 180 mm. of water. In a third patient, not included in the table because the patient died before the cardiac output could be measured, the atrial pressure was 180 mm. of water. R. B. had a very high atrial pressure with a normal cardiac output. He had received 500 c.c. of blood and 1,000 c.c. of physiologic saline solution before the atrial pressure was measured. The rise in venous pressure in the untreated patient with acute pericardial tamponade results from a redistribution of blood within the vascular tree and from vasoconstriction.⁵ A small amount of blood may be shifted from the arterial to the venous system as the arterial pressure falls, and blood within the venous system may be redistributed by constriction of the smaller vessels so that the pressure in the venous system rises. The height to which the venous pressure rises will be determined by the ability of the veins to constrict and by the quantity of blood in the vascular bed. The factors causing the venous constriction have not yet been determined.

If the blood volume is reduced by hemorrhage the venous pressure rise will be lessened. In patients with chronic congestive failure the rise in venous pressure results in part from the increase in blood volume.⁵ Because the blood volume is usually somewhat decreased by hemorrhage and is never increased in patients with stab wounds of the heart, the venous pressure in these patients with sudden tamponade usually does not reach the extreme heights to which it may rise in chronic congestive heart failure.

If the blood volume is raised by giving blood or other fluids intravenously the venous pressure can be increased above the level present before treatment. The high atrial pressure in R. B. was probably the result of the blood and saline solution which he received prior to our studies. The question has been asked as to whether raising an already elevated venous pressure by giving of fluids intravenously will benefit the circulation in patients with stab wounds of the heart. The problem has been approached experimentally in two laboratories. In one⁷ a further rise in venous pressure was found to be beneficial; in the other⁷ no improvement was observed. It is clear that a rise in venous pressure will not improve the circulation unless the heart is able to receive more blood during diastole. This will be possible only if the increased atrial and pericardial pressures either cause the pericardium to stretch or force some of the blood out of the pericardial sac. The results of administering fluids intravenously in the clinic led us to believe that a further rise in venous pressure was beneficial.

Quantitative studies in two patients showed some but not a striking improvement when the atrial pressure was raised above the level present on admission by the use of human albumin solution (Fig. 2).

The relation between the cardiac output and the arterial pressure in the four patients with low cardiac indices (two with stab wounds of the heart and two with pericardial effusion) showed no evidence of arteriolar dilatation. The peripheral resistance was in the high normal range in all of these patients. This high peripheral resistance is similar to that seen in patients with circulatory failure from acute hemorrhage¹ and is in sharp contrast to the low peripheral resistance seen in patients with circulatory failure from reflex stimulation of the pleura from a penetrating wound of the chest.⁴ A rise in peripheral resistance with a falling cardiac output is also characteristic of congestive heart failure.⁸

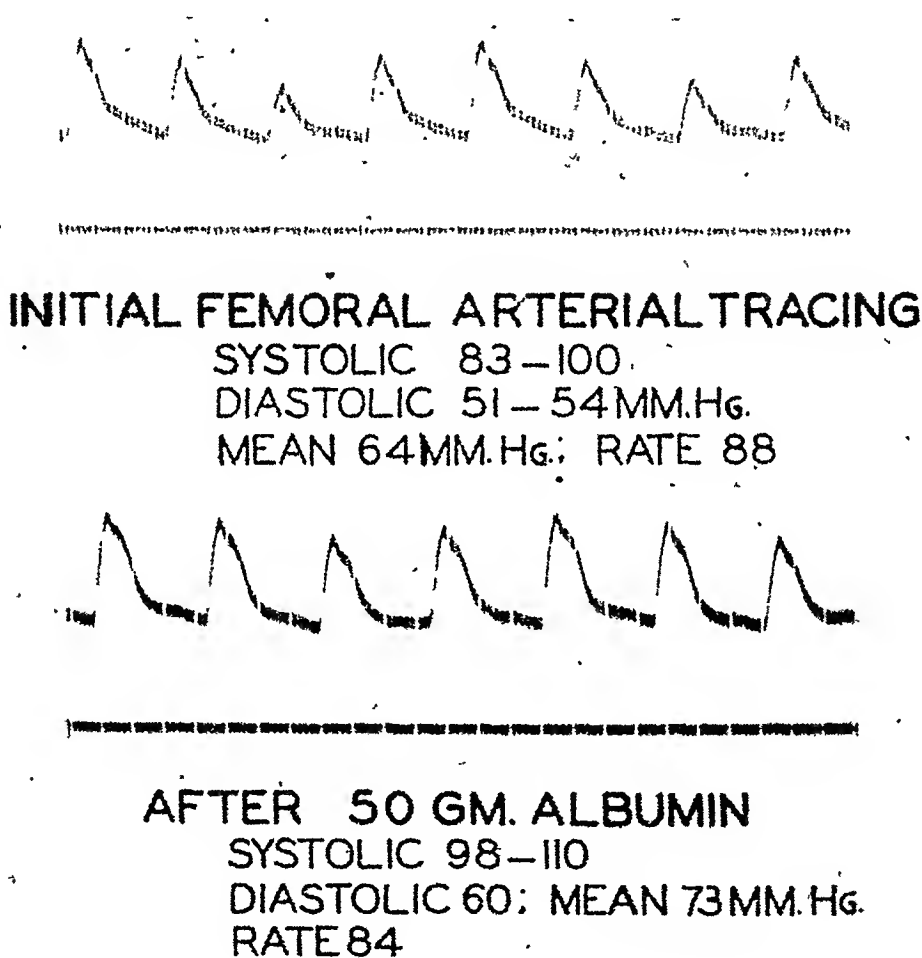


Fig. 2.—Femoral arterial pressure tracings of patient S. W. who had pericardial tamponade as result of a stab wound of the heart.

The patients with massive pericardial effusions were severely ill. They showed the same disturbances in the circulation which were found in the patients with tamponade from stab wound of the heart. In the two patients with the greatest decrease in cardiac output, the peripheral resistance was in the high normal range. The atrial pressure fell very slowly during aspiration of the pericardial sac, remaining above normal after as much as 1,100 c.c. of fluid were removed. The reason for this slow fall in pressure was not established. It is

possible that the pericardial pressure was still elevated sufficiently to account for the high atrial pressure. These patients had been in circulatory failure for some time and a rise in blood volume may have occurred as happens in persons with prolonged circulatory insufficiency from heart failure.²

Since aspirating the pericardium produces such dramatic improvement in patients with pericardial tamponade from large effusions, it seemed logical to attempt this procedure in patients with tamponade from a stab wound in the heart. In one of the patients reported here and in two not reported because complete data were not obtained, aspiration was not successful. At operation or autopsy the blood in the pericardium in these three patients was found to be clotted. In two patients not included in this report aspiration was successful. In both of these the aspiration was done immediately after the patient entered the hospital without waiting for detailed studies on the circulation.

The following routine has now been established in the emergency clinic at Grady Hospital. The patient is given an infusion of saline solution and is fluoroscoped immediately. If he has the clinical and x-ray signs of pericardial tamponade, aspiration is attempted at once. The patient receives a transfusion and the operating room is set up. If the aspiration is unsuccessful or if the signs of pericardial tamponade recur after a successful aspiration, the heart is sutured.

SUMMARY AND CONCLUSIONS

1. The disturbances in the circulation produced by pericardial tamponade have been studied by the method of right heart catheterization. Four patients had stab wounds of the heart and three had pericardial effusion or empyema.

2. The circulatory failure observed in patients with stab wounds of the heart may be caused either by pericardial tamponade, by reflex arteriolar dilatation, or by both. Tamponade causes a decrease in cardiac output and a fall in arterial pressure without arteriolar dilatation. The relation between the cardiac output and the arterial pressure is similar to that observed in patients with circulatory failure from acute hemorrhage.

3. Paradoxical pulse, elevated venous pressure, and decreased pulsation of the borders of the heart on fluoroscopic examination may occur before other signs of circulatory failure are present.

4. The height to which the venous pressure rises in acute pericardial tamponade depends on the size of the blood volume and the degree of venoconstriction. Therefore, there will be no rigid correlation between the degree of circulatory failure and the height of the venous pressure.

5. Raising the venous pressure by increasing the blood volume through the rapid intravenous infusion of human albumin solution appeared to cause some improvement in the two patients in whom quantitative data were collected. This is in agreement with our clinical impression from observing the results of treating a larger group of patients in whom quantitative data were not obtained.

6. Aspiration of the pericardium is a satisfactory method of relieving pericardial tamponade in certain patients with stab wounds of the heart. It

should be performed as quickly as possible because the blood in the pericardium will clot.

7. The changes in the circulation in patients with tamponade from empyema or chronic effusion of the pericardium are similar to those observed after stab wounds of the heart. The atrial pressure fell slowly as the pericardial fluid was removed and in one instance remained elevated after 1,100 c.c. of fluid were removed.

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THE EFFECTS OF MALARIA ON THE HEART

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ALTHOUGH it is probably true that malaria is the most widespread and serious disease in the world, this knowledge had not had a proportionate influence upon medical thinking in the United States until our experience in the Pacific during World War II brought the problem to the fore. Of the so-called tropical diseases brought back to us from the combat areas, malaria is the one about which there arise the most frequent questions. There is concern not only about the public health aspects of malaria, but also about its permanent effects upon individuals infected with the plasmodia.

Though malaria is a disease from which no organ or tissue is exempt, this paper is concerned with its influence upon the circulation, and more particularly upon the heart itself. Of the characteristics peculiar to malaria, those which might be expected to affect the heart are (1) its chronic and recurrent nature, (2) the systemic toxemia of the paroxysm, (3) the profound anemia produced by hemolysis and suppression of hemopoiesis, and (4) the occlusion of capillaries and arterioles of the myocardium. The published clinical and pathologic studies of malaria indicate that these are, in fact, the mechanisms involved.

REVIEW OF LITERATURE

Medical literature, especially that from France, Italy, and Latin America, abounds with references to a great number of cardiovascular injuries attributed to malaria. While in general these references seem to be a mass of supposititious material, it must be conceded that the implications in these papers are partly based on observations of long-standing, inadequately treated cases which would not be seen in our Army, Navy, and Marine Corps personnel.

Long before the malarial parasite was discovered in 1880, it was believed that the heart was frequently injured by the disease.¹ Laveran published a description of such cases, and in 1890 they were summarized by Ranzier. Duroziez reported instances in which malaria had produced various valvular and myocardial changes in which pigmentation was prominent. Tremolières and Causade described aortic, coronary, endocardial, mural, and arterial injuries in acute and chronic cases of malaria. They found 42 cases of patients with cardiac involvement among 1,000 patients with malaria. In 17 of these 42 cases, the involvement was functional: four had precordial pain; four, palpitation; three, breathlessness; and five, permanent, and one, paroxysmal, tachycardia. Castellani reported a case of heart block in a middle-aged man cured by the use

The opinions contained in this article are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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of quinine and three cases of angina pectoris cured by the same drug. Lanceraux quotes the case of a woman 34 years of age with angina pectoris and a double aortic murmur which he believed were due to malarial aortitis.

It is of interest to remember that the "de Musset sign," nodding of the head with each heart beat when there is pronounced aortic regurgitation, was named for Alfred de Musset by his brother, who ascribed his aortitis to malaria acquired in Italy.

Recent writers have described electrocardiographic changes in malaria, including right bundle branch block (old terminology) and T-wave changes.^{2, 3}

EFFECTS OF MALARIA ON THE CIRCULATION

Clinical Aspects.—The effect of malaria on the circulation differs with the stage and severity of the disease. In malarial damage to the brain, it has been our experience that functional cerebral disturbances most often occur and true "cerebral malaria" in which thrombosis of the brain capillaries is the characteristic pathology occurs but rarely. So in cardiac malaria a series of functional aberrations may be commonly found, but the syndrome of heart failure is very infrequent. Gaskell and Millar, in a review of their experience in World War I⁴ with very severe cases of malaria in Serbians, divided the fatal cases into the true cerebral, the septicemic, and the cardiac types. They stated that, "The cardiac type is only likely to be fatal when hospital arrangements have to cope with an overwhelming number of serious cases."

It was shown by Brown and Loevenhart (1913)⁵ that the injection of alkaline hematin into dogs and cats caused dilatation of the splanchnic vessels, constriction of cutaneous vessels, and marked fall in blood pressure. The slowing of the heart and reduction in cardiac output are due mainly to the toxic effect on the vasomotor and cardioinhibitory centers.

Meleney⁵ states that serious circulatory disturbances in man occur almost entirely in falciparum infection. Before the paroxysm there are a vagal bradycardia, lowered blood pressure, and slight miosis.¹² During the cold stage there is an increasing sympathetic effect, with a return to vagotonia during the sweating stage. Tachycardia and premature beats may be manifestations of a direct toxic effect of malaria on the myocardium, and may persist in the chronic phases of the disease. Manson-Bahr, in 1920, said, "The most acute cases die of heart failure, apparently a toxæmic myocarditis."⁶

Pathologic Findings.—Pathologic studies of the heart in fatal malaria have been extensive. Over 40 years ago Ewing⁷ described the dilated, pale, or slightly brownish-tinged heart muscle with perinuclear masses of greenish pigment in the cells. In one exceptional case the distended capillaries of the heart wall were filled with young parasites and pigmented cells. In 1917 at Salonica Dudgeon and Clarke⁸ found myocardial changes in malaria similar to those of diphtheritic myocarditis. Of their 45 fatal cases, 23 showed fatty degeneration of the heart muscle. There was also blocking of the capillaries and arterioles, local hemorrhage, and deposit of pigment. Fragmentation of the muscle may be extreme. Gaskell and Millar found the subtertian parasites among or

within the cardiac muscle cells. In chronic cases there may be fatty degeneration especially of the muscle of the left ventricle. This has even resulted in cardiac aneurysm or rupture of the ventricle.⁶ Gallenga⁷ described primary degenerative changes in the cardiac nerves in a case of angina pectoris of malignant tertian origin. Anderson¹ believes that malaria has two cardiac effects, that on the extrinsic vagosympathetic nerves and a direct intracardiac neuritis. Seyfarth,⁶ in his detailed paper on the pathologic anatomy of malaria, found that cardiac deaths comprised about 14 per cent of the malarial fatalities; septicemic deaths, 30 per cent; cerebral deaths, 55 per cent; and renal deaths, 1 per cent. He described the pathology of the cardiac type as consisting of blockage of the coronary radicles with parasites and pigment, and either a toxic myocarditis or heart muscle necrosis, or fatty change with especial involvement of the conduction system. -

In describing the effects of malaria on the peripheral vascular system, the older writers describe malarial arteriosclerosis, obliterative endarteritis, venous thrombosis, and the previously mentioned "aortite paludéene."

Contemporary authors generally agree, however, with the recent statement of Cannon¹⁰ that the reticulo-endothelial system is most commonly affected in malaria, and that the myocardium and other organs are rarely affected. Endothelial phagocytosis fortunately occurs mainly, if not wholly, in the spleen, liver, and bone marrow. Furthermore, it must be emphasized that the malignant tertian (*falciparum*) malaria parasite is the predominating organism in fulminating, vascular occlusive, fatal malaria regardless of the type of terminal process. ✓

EXPERIENCE WITH SOUTH PACIFIC MALARIA

The author served as Chief of Medicine in a Naval Mobile Hospital in New Zealand for a year between Aug. 7, 1942, when the Marines started the Solomon Islands Campaign, and August, 1943, when he joined a hospital ship in the South Pacific Area. Since January, 1944, he has been Chief of Medicine in a large continental Naval hospital. These posts have permitted observation of malarial patients from the early days of their infection to a time almost three years later, when the men with relapses are still being admitted to the hospital. Although many thousands of patients with malaria have passed through these medical services, there has been no clear-cut case of malarial heart disease. The most severe cases of malaria, of course, were seen in New Zealand in Marines from Guadalcanal. At this time prophylaxis, therapy, and malaria control were not well understood.¹¹ "Although three patients died from malaria with cerebral manifestations, there was no specific pathology in the heart at autopsy. The only patient showing clinical cardiac effect was one who, during intravenous quinine therapy, developed probable complete A-V block with ventricular fibrillation. The electrocardiogram taken after the patient had responded to intravenous adrenalin showed auricular paroxysmal tachycardia with right axis deviation. The patient made a complete cardiac recovery. ✓

Patients with many relapses of vivax malaria continue to enter Naval hospitals in the United States. We have observed approximately 2,000 relapse ad-

mission cases in the past sixteen months. In none of these patients with chronic relapsing malaria was any cardiac condition discovered which could be specifically attributed to malaria. Any chronic disease, especially one resulting in anemia, may produce the symptoms of irritable heart with tachycardia and premature beats. Functional systolic murmurs may be found but even these have not been common among the patients at the hospital.

A series of 50 cases of recurrent malaria, all but one of the vivax type, were studied electrocardiographically.* All of the patients had had recurrent malarial attacks, some over a period of thirty-three months. Two had cerebral symptoms indicating a probable organic change caused by vascular occlusion and resulting in the malarial encephalopathy syndrome. The electrocardiograms were often recorded directly after the chill, while the patient was still febrile. Some of the patients had had over a dozen relapses. One patient, in addition to eleven recurrences, had had scrub typhus and scarlet fever, but the cardiac findings were normal. In two typical patients observed directly after the chill the electrocardiograms were normal, and the pulse rates were 76 and 78. The one patient with falciparum parasites in the blood had acquired the infection three months before on the west African coast. Again there were no cardiac abnormalities.

Among the entire group of 50 patients there was no electrocardiographic finding which could not be considered either within normal variants or of non-specific import. In tracings of malarial patients studied in the various Naval activities mentioned, we have recorded ventricular and auricular premature beats, low T waves associated with anemia, nodal tachycardia, right axis deviation of slight degree, sinus bradycardia and tachycardia, and a P-R interval of 0.21 second. ✓

DISCUSSION

From the evidence presented in the literature it seems justifiable to consider that malaria, especially of the malignant tertian type, may rarely be fatal by its direct myocardial effect, which is either toxic or anoxic through coronary capillary occlusion. On the other hand, even when malarial patients die from septicemic or cerebral mechanisms, the heart seems to be very infrequently affected. ✓

There is also evidence in the literature that prolonged relapsing malaria in natives of malarious countries may result in chronic cardiac disturbances, which may progress even to the point of cardiac dilatation, ventricular aneurysm, and cardiac rupture. In chronic malaria the influence of malarial cachexia, which is a complex nutritional and hemoclastic affair, accompanied by widespread pigment deposit throughout the body and by capillary occlusion, may produce changes in the circulation indistinguishable from those of chronic anemia. There is no evidence of critical value to show that valvular heart disease or aortitis results from malaria.

The possibility that members of our own Armed Services may develop cardiac pathology from recurrent malaria is very remote. Our men are treated

*This was done with the cooperation of Commander William A. Coates, M.C., USNR, in charge of the malaria service.

early and adequately; the factors of malnutrition, avitaminosis, anemia, and complications (such as blackwater fever) are vigorously attacked, and hospitalization is readily available.

CONCLUSIONS

✓ According to the literature heavy plasmodial infection (especially with *Plasmodium falciparum*), or untreated or inadequately treated malaria can cause death from myocardial inflammation or capillary infarction, and chronic recurrent malaria can produce myocardial pathology similar to that caused by prolonged anemia. However, malaria, in our experience with several thousand cases occurring in members of the Armed Forces of the United States, has resulted neither in acute cardiac death nor in any proved chronic cardiac disease.

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FURTHER OBSERVATIONS ON THE USE OF MERCUPURIN ADMINISTERED ORALLY

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SINCE the presentation of the original report¹ on the oral use of Mercupurin, additional information concerning its value for the treatment of congestive heart failure has become available. It must be stressed that the oral administration of a mercurial diuretic is not recommended to replace the intravenous preparations. We are not concerned with the comparative potency of the oral and parenteral preparations in the same patient, for there is no doubt that the intravenous preparations are superior to oral preparations and are more reliable in producing a diuresis. However, many patients can be benefited by the oral use of a mercurial. This investigation was, therefore, undertaken in an effort to answer the following two questions: (1) Is the mercurial diuretic in the form administered orally an effective and safe diuretic for relieving the signs and symptoms of congestive heart failure present in the average patient? (2) If the oral preparation is effective, how should it be administered in order to obtain its maximum value? Factors such as degree of edema, severity of the heart disease, the effect of the concomitant administration of other medications, and the question of whether the patient is ambulatory or bedridden must be carefully considered.

The oral preparation of Mercupurin* was studied in both hospitalized and ambulatory patients, according to several plans. Although the single and multiple dose methods of administration have already been reported, for the sake of completeness, summaries of our experiences with all methods of administration have been included in this report. A total of 81 patients presenting all stages of congestive heart failure were given Mercupurin orally. Fifty-six were treated exclusively as hospitalized patients, five were observed as both hospitalized and ambulatory patients, and 20 were treated solely as ambulatory patients.

The method for studying diuretics which has proved most satisfactory in our hands has been presented previously.²⁻⁴ A practical and relatively quick appraisal of the effectiveness of a diuretic can be gained in hospitalized patients by administration of the preparation after a preliminary period sufficiently long to evaluate concomitant therapeutic measures, such as bed rest, digitalization,

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*Each tablet contains 120 mg. of Mercupurin, which is equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline, whereas 1 c.c. of the parenteral solution contains 135 mg. of Mercupurin. Mercupurin tablets were supplied by Campbell Products, Inc., New York, N. Y.

or the effectiveness of other diuretic agents. The length of this control period depends upon the condition of the patient and may vary between three days and several weeks. As a rule, when a patient is hospitalized for severe congestive heart failure, he is watched constantly for any change in clinical status. If he becomes worse he is given the diuretic immediately. The majority of patients, however, are observed for several days in order to exclude the spontaneous diuresis which so often occurs after a few days of bed rest. Patients who respond to digitalization are not given the diuretic. If digitalis alone no longer produces satisfactory diuresis, the mercurial is administered after the maintenance dose of digitalis has been established. If improvement is evidenced by the weight curve, it can be assumed, especially if consistent results are obtained in a majority of the patients, that the diuretic was responsible for the improvement. A diuretic response is considered to be an effective one if the patient loses at least three pounds of edema fluid. In the single dose method, this response should occur within forty-eight hours. When the multiple dose method is used, the diuresis should occur during the period of administration, or at least no later than twenty-four hours after the drug is discontinued.

I. Single Dose Method.—In an effort to determine whether or not Mercuripurin administered orally in a single dose could produce an effective diuresis, five tablets (a single dose) were given to 24 patients, some of whom were treated more than once, for a total of 31 trials. A satisfactory response was obtained in 18 trials (58 per cent), or 16 patients (67 per cent). Diuresis usually began within four to twelve hours, and with few exceptions was completed in less than twenty-four hours. This method of administration is not reliable and the degree of diuresis obtained by its use does not approach that produced by the intravenous preparation.

II. Multiple Dose Method.—One to three tablets three times daily for a period of two to five days constituted a trial or course of treatment. Thirty-nine such courses were given to 29 patients. A satisfactory response was obtained in 25 trials (67 per cent), or 20 patients (69 per cent). Diuresis was usually slow in developing and in many patients did not reach its peak until the drug had been given for forty-eight hours. Nevertheless, the total diuretic response frequently approached that achieved with an intravenous preparation. This method is not the one of choice when rapid removal of edema fluid is desired. It is, however, the ideal method for patients who do not require emergency measures, for those who should have the edema fluid removed gradually, and for those who cannot be given the diuretic parenterally.

In considering the seemingly high percentage of failures in our study, it must be emphasized that in evaluating the effectiveness of any new drug, consideration must be given to concomitant therapeutic procedures. For this reason digitalis or ammonium chloride was deliberately withheld in several trials. We would undoubtedly have obtained a much higher incidence of effectiveness if the patients had been given these or other drugs. Our studies convinced us that previous digitalization and the maintenance of digitalis effects, as well as simultaneous administration of ammonium chloride, are desirable when an oral diuretic is used. We believe that unsatisfactory responses oc-

curred only in those patients who had a minimal degree of heart failure or in those whose heart disease was so severe that only a parenteral preparation could have resulted in diuresis. The use of the oral preparation is contraindicated when the response to the previous administration of a parenteral diuretic was unsatisfactory. Not only would the oral preparation be of no avail, but it might produce untoward reactions. Similar situations are encountered in the treatment of bronchial asthma with various epinephrine derivatives. For instance, epinephrine in oil cannot be expected to give relief when aqueous epinephrine hydrochloride has proved to be ineffective.

The slower diuresis produced by the oral mercurial administered by the multiple dose method is indicated in many patients. The oral method also enables the physician to treat patients to whom it is difficult to administer the drug by injection. Although the immediate diuresis may not be great, the effect of the oral Mercupurin may be more prolonged than that produced by the parenterally administered drug. Thus, patients who reaccumulate edema rapidly and for this reason require intravenous medication at frequent intervals, may accumulate their edema at a much slower rate, or not at all, when given the oral preparation. A diuretic with a slow but definite diuretic effect seems to allow the patient's heart to compensate to a greater degree.

The multiple dose method has particular value in the treatment of ambulatory patients. For those patients who require a mercurial diuretic only occasionally and whose congestive heart failure is not too severe, the use of the oral preparation makes fewer clinic visits necessary. The dose and scheme of administration must be determined for each patient. Once these are established, the patient readily learns the most propitious time for self-administration of the tablets.

In 10 of the 13 ambulatory patients studied, the response was considered to be satisfactory. Out of 152 trials, only eight resulted in an ineffective response. However, it should be remembered that the majority of the trials were in patients whose initial responses were favorable, and the drug was, therefore, continued as required. Thus, two patients (3 and 7, Table II¹) with advanced rheumatic heart disease have taken 32 and 44 courses, respectively, and have remained very well controlled as ambulatory patients for over two years, while, with the use of the intravenous preparation, they had spent several weeks or months of each year in the hospital.

Toxicity with the multiple dose method was of little consequence in hospitalized patients. Mild gastrointestinal irritation of a transient nature was observed in only two of the 29 hospitalized patients. The ambulatory patient seemed more prone to develop gastrointestinal irritation, since it was noted in 6 of the 13 patients so treated. The characteristics of these reactions have been discussed in detail previously.¹ Such reactions do not usually limit the usefulness of the drug, since they may not recur upon repeated trials. No explanation for the higher incidence of gastrointestinal irritation in the ambulatory patients has been found. However, we have observed that many other drugs cause more untoward reactions in ambulatory patients than they do in hospitalized patients.

Evidence of kidney irritation was observed in only one of the 42 patients treated by the multiple dose method. This consisted of an increasing albuminuria after nineteen months of therapy which included 26 trials of one tablet three times daily for three-day periods. Since there was no evidence of generalized mercurialism and since the specific gravity of the urine revealed good concentrating ability, the presence of albuminuria was not considered to contraindicate the continuation of therapy.

III. Daily Dose Method.—The daily maintenance dose of Mercupurin administered orally was followed in 26 hospitalized patients for 30 trials and in 18 ambulatory patients for 31 trials. All of these patients were in progressively severe congestive heart failure which no longer responded to a maintenance dose of digitalis. With few exceptions all had been receiving frequent injections of Mercupurin intravenously. These injections brought temporary relief but did not prevent the reaccumulation of the edema. The 26 hospitalized patients received two tablets in an undivided dose for periods of seven to forty-one days (average period, nineteen days). The ambulatory group of patients have, to date, received from one to two tablets daily for periods of one to forty-nine weeks (average period, sixteen weeks) of continuous therapy. The patients of both groups were observed with and without the additional administration of ammonium chloride. In several instances the value of ammonium chloride was demonstrated by instituting its use after it was apparent that diuresis would not be produced by the administration of Mercupurin alone. It soon became evident that patients in severe congestive heart failure required several days of oral Mercupurin therapy before diuresis occurred. In those ambulatory patients who had been receiving Mercupurin intravenously at intervals of three to four days or a week, it was necessary to continue this regime until the oral drug became effective. To avoid undue overloading of the kidneys with mercury, it is recommended that no greater dose than 1 c.c. of the parenteral preparation be used. This procedure also avoids the tremendous diuresis, amounting in some patients to as much as 15 to 20 pounds of fluid, and the likelihood of complications or sequelae, which may occur when the usual parenteral dose is administered after the oral administration of 30 or 60 mg. of inereury for several days.

The patients who responded to the daily dose required from four to fourteen days (an average of seven days) of continuous therapy before the medication became effective. Of the 26 hospitalized patients complete removal of the edema and alleviation of acute symptoms such as paroxysmal dyspnea were obtained in 15 patients who had been previously uncontrolled. In four patients the diuresis was insufficient to alleviate completely the signs and symptoms of congestive heart failure, but definitely improved the cardiac status so that either intravenous mercurial diuretics were required less frequently or delayed the reaccumulation of the edema. An effective diuresis was, therefore, attained in 73 per cent of the hospitalized patients.

In the ambulatory group (18 patients) the results were even more gratifying, with effective diuresis being produced in 77 per cent of the patients. Ten patients with marked congestive heart failure, who attended clinic regularly

for weekly or biweekly injections of Mercupurin, became edema-free and presented minimal or no signs of decompensation. The status of four of the patients was improved: the edema did not reaccumulate as rapidly as before, and the necessity for intravenous mercurial diuretics was decreased.

The oral administration of Mercupurin failed in seven hospitalized and four ambulatory patients. Failure could be attributed in most cases to the severity of the heart condition, since eight of the 11 patients died shortly thereafter in spite of all efforts to induce diuresis. All eight of these patients also stopped responding to the intravenous mercurial diuretics. When a parenteral preparation no longer induces an effective diuresis, it is only natural to try other means of therapy. However, for such patients oral Mercupurin is of no value, and its use may result in mercurialism. Other reasons for failure were insufficiently long periods of treatment and the omission of the simultaneous administration of ammonium chloride.

Toxicity associated with the daily dose assumed several forms. The most common untoward reaction was digitalis toxicity related to the phenomena of mobilization of the digitalis from the edema fluid at the time of diuresis.⁵ Thus, digitalis toxicity invariably occurred after diuresis was well established, i.e., after four to fourteen days of daily dosage, when the existing edema was in the process of being removed. Digitalis toxicity was observed in five of the hospitalized patients (19 per cent) and in six of the ambulatory patients (33 per cent); 11 of the 44 patients (25 per cent) receiving the daily dose. The classical signs of digitalis toxicity were observed. The rhythm changed from normal sinus rhythm to auricular fibrillation (four instances); there was a marked slowing of the ventricular rate of an underlying auricular fibrillation (four instances); A-V conduction time, as measured by the P-R intervals, increased to the level of partial block (two instances). However, when there was anorexia, nausea, vomiting, or diarrhea, it was difficult to decide whether the disturbance was due to gastrointestinal irritation from the oral Mercupurin or was a symptom of digitalis toxicity. Proof that these reactions were caused by digitalis toxicity was obtained when it was found that the gastrointestinal symptoms of all these patients subsided completely when digitalis was discontinued or decreased, even though the oral Mercupurin was administered uninterruptedly. Therefore, all patients presenting gastrointestinal symptoms, whether or not they presented the classical unequivocal signs of digitalis toxicity, were subsequently treated with smaller maintenance doses of digitalis. We have no doubt that true gastrointestinal irritation caused by the daily dose of oral Mercupurin may be encountered, although it was not observed in our series of patients.

Of more importance is the early recognition of mercurialism. Gastrointestinal symptoms associated with increasing albuminuria occurred in three instances. This occurred usually within a few weeks of the institution of therapy and only in patients who had already presented evidence of kidney disease. In one of these three patients these symptoms were associated with severe gingivitis and elevation of the nonprotein nitrogen. All of these manifestations subsided when the diuretic was discontinued. Four other patients presented in-

creasing albuminuria, but only after continuous therapy for more than thirty weeks. Fear of impending generalized mercurialism prompted the cessation of therapy in these four patients. However, they returned to the clinic or hospital in such severe congestive heart failure that administration of the oral diuretic was reinstituted in spite of the albuminuria. None of these patients demonstrated other signs of mercurialism. Not only did they continue to have a favorable diuretic response, but, even after additional therapy for as long as twenty weeks, they did not develop additional toxicity. Our experience with these patients and with many other patients who presented albuminuria before therapy was begun but did not develop further toxicity, leads us to believe that albuminuria per se does not contraindicate the continuation of the use of mercurial diuretics. These patients should, of course, be carefully observed for early signs of generalized mercurialism. It is our present policy, after the maximum effect of the oral diuretic has been achieved, to allow the patient a rest period of one week, and then to continue the diuretic for one month. Short rest periods are given between each monthly course.

Mild gingivitis was observed in four patients (9 per cent, including the patient already discussed). The gingivitis subsided promptly when therapy was discontinued. Two of the patients, given the oral therapy a second time, did not develop toxicity.

The most serious complication was the occurrence of uremia. The non-protein nitrogen became elevated in two of the hospitalized patients. Following thirty-two days of continuous therapy, the first patient (already discussed) had a rise of the nonprotein nitrogen to 52 mg. per cent. After twenty days of continuous therapy the second patient, a 70-year-old woman with arteriosclerotic heart disease, became stuporous. This was associated with nausea, vomiting, and elevation of the nonprotein nitrogen to 112 mg. per cent. Prior to the appearance of these symptoms, a good diuresis had been obtained, in spite of a fixation of specific gravity of the urine. When the medication was discontinued, the nonprotein nitrogen returned to normal limits, but the patient reaccumulated the edema. A second trial consisting of twelve days of therapy again produced diuresis and an elevation of the nonprotein nitrogen to 90 mg. per cent. At no time did the patient show albuminuria or gingivitis. In the light of this experience, we believe that the oral mercurial should not be used in any patient who presents impaired kidney function, such as fixation of urinary specific gravity.

COMMENTS

The results indicate the value of the maintenance dose of Mercupurin administered orally in the treatment of patients with congestive heart failure. We feel that the effectiveness of the method outweighs the possibility of the occurrence of toxic reactions. It has its greatest usefulness in patients with congestive heart failure who have exhausted the value of a maintenance dose of digitalis and who, in spite of repeated injections of a mercurial diuretic, reaccumulate their edema or experience a recurrence of acute symptoms. The oral diuretic will remove all signs and symptoms of failure in such patients

making it possible either to dispense with the intravenous preparation or to decrease the number of injections required. We have never been able to achieve these results with any of the oral xanthine derivatives. Only since we have been using mercurial diuretics orally have we been able to improve the general status as well as the morale of patients with severe congestive heart failure and to make these patients continuously comfortable.

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MASSIVE LEFT AURICLE WITH SPECIAL REFERENCE TO ITS ETIOLOGY AND MECHANISM

REPORT OF A CASE

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MASSIVE dilation of the left auricle of such an extent that this chamber actually formed a part of the right border of the heart was described in 1901 by Owen and Fenton.¹ Since that time, there have been a number of such cases reported.¹⁻¹⁷ In reading these various papers we have been impressed chiefly with the various suggestions as to the possible causes of such enormous left auricles and the apparent benign course that the disease takes before heart failure appears.

The heart in the case that we wish to report, while similar to others discussed in the literature, is apparently one of the largest recorded, weighing 1,600 grams and containing over 2,000 c.c. of blood. Hearts weighing over 1,000 grams are considered rare since less than 50 cases have been recorded in the literature in the last one hundred years.¹⁸ The relatively few reported cases are not, however, an accurate measure of the frequency of large hearts. Large hearts are not infrequently seen in any large autopsy service; one of us (H. S. M.) has in the museum of the Newark City Hospital a rheumatic heart with aortic regurgitation and mitral insufficiency weighing 1,250 grams, a syphilitic heart with aortic regurgitation weighing 1,160 grams, an hypertensive heart weighing 900 grams, and a heart with primary sarcoma weighing 1,500 grams.

Massive left auricle is considered by most authorities as a rare or unusual condition. We believe, however, that it is more frequent than thought to be.

CASE REPORT

History.—W. M., a 33-year-old white man, while sitting quietly at home, suddenly complained of sub-sternal pressure, gasped, and died within a few minutes. When 8 years of age he had had his first attack of rheumatic fever, with a typical migratory polyarthritide involving most of the joints of his extremities. Between the ages of 8 and 14 years he had had recurrent, mild attacks of arthritis every spring. These illnesses usually lasted about two months and gradually cleared up with the approach of summer. When he was 10 years of age his tonsils were removed, although he had had no sore throats or frequent colds. When he was 15 years of age an infected supernumerary tooth in the left upper jaw was removed along with a portion of the bone which was also infected. After this operation,

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all arthritic attacks ceased, except for slight stiffening in one joint or another during damp weather. The patient was told at this time that his heart was affected. However, he had no cardiac symptoms. At the age of 15 he became a plumber's apprentice and, after four years, a journeyman plumber. During the next five years he engaged in amateur boxing, taking on bouts almost weekly without undue dyspnea or fatigue. He ran 5 or 6 miles two or three times a week without any difficulty. When 18 years old he ran to the top of the Washington Monument in fifteen minutes. His only reaction at the end of the climb was slight shortness of breath for several minutes and marked fatigue of his legs for about half an hour.

At the age of 29 he first began to have difficulty with his heart. He developed a short, hacking, nonproductive cough which he attributed to cigarettes. On one occasion he coughed up a small amount of bright red blood and was hospitalized for five days. His cough then ceased, and he returned to work. When 31 years of age he began to be dyspneic on slight exertion, and slight edema of the ankles appeared. After three days of particularly strenuous work which involved the use of a 15-pound sledge hammer, he developed severe dyspnea and orthopnea with generalized edema. This condition improved considerably after two weeks rest in bed, and he returned to work. In a short time, however, he had another severe break in compensation which necessitated two and one-half months of bed rest and digitalis therapy. After this episode breathing began to be associated with sharp, severe pains which radiated up and down the sternum. He also became conscious of his heartbeat. To make matters worse, the patient developed difficulty in swallowing with the result that two or three minutes were required for a bolus of food to pass through the esophagus.

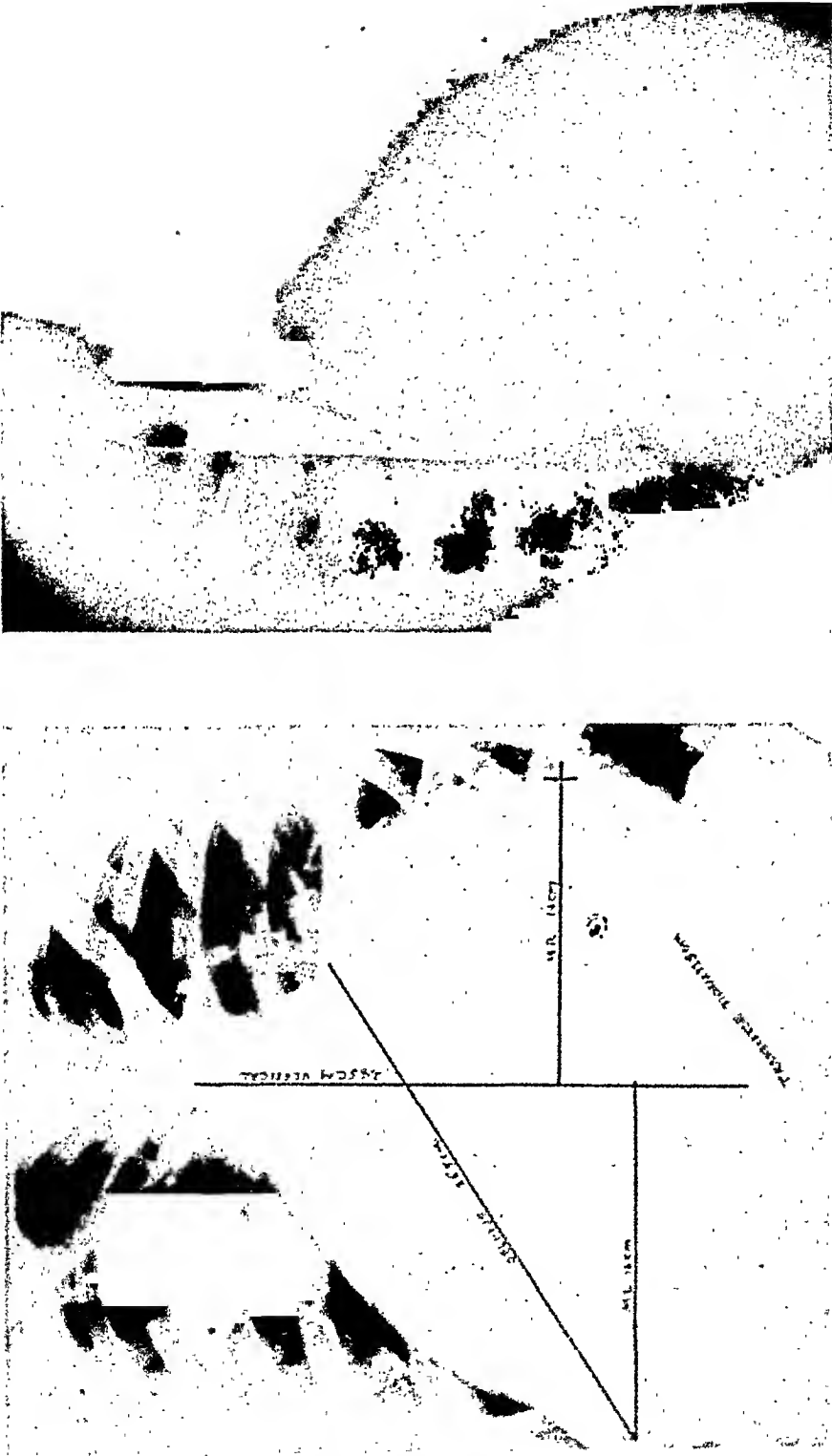
Six months after the onset of cardiac symptoms, the patient was admitted to the Newark Beth Israel Hospital.

Examination.—On initial examination the patient was sitting up in bed, and appeared to be fairly comfortable. There was no cyanosis, edema, or clubbing of the fingers. The blood pressure was 130/70 in both arms. The apex impulse was 16 cm. to left of the midline in the seventh intercostal space. A precordial heave was observed with each heart-beat. The heart sounds were of fair quality. Auricular fibrillation with a slow ventricular rate and no pulse deficit was present. A harsh, loud, systolic murmur was best heard in the region of the left nipple. The murmur was transmitted to the left axilla and down to the eighth rib in the anterior axillary line. This murmur obliterated the first sound but did not replace the second sound. About 1 inch below and to the right of the left nipple, this systolic murmur became musical and whistling in character and was heard to the midline. Just to the right and below the left nipple, a short, rumbling, loud presystolic mitral murmur was heard which was not transmitted. Over this same area a presystolic thrill was felt. Over the aortic area a short, musical, diastolic murmur, just preceding systole, was present. A very soft, short, blowing, systolic murmur was also heard in the same area. Over the tricuspid area a soft systolic murmur, replacing the first sound, was heard. Only occasionally was a systolic murmur elicited over the pulmonary area. Though these murmurs were generally demonstrable, they were not constantly present.

The remainder of the physical examination was essentially negative. During his stay in the hospital the temperature was normal, the pulse ranged from 40 to 88 per minute, and the respirations were 20 per minute.

The urine, blood count, and blood chemistry studies were normal, and serologic tests for syphilis were negative.

Subsequent Course.—After three months' stay in the hospital he was discharged as improved with the clinical diagnosis of "rheumatic heart disease with massive left auricle." During the next six months he had three attacks of decompensation which necessitated three short periods of hospitalization. In the intervals, he was kept fairly comfortable by small doses of digitalis and much rest and was able to do some very light work. His weight remained normal, he ran no fever, and he developed no anemia. Except for an occasional small hemoptysis and some substernal pain, which occasionally was severe and radiated to



A.
B.
Fig. 1.—Teleoroentgenograms showing massive left auricle. Anteroposterior and right lateral views.

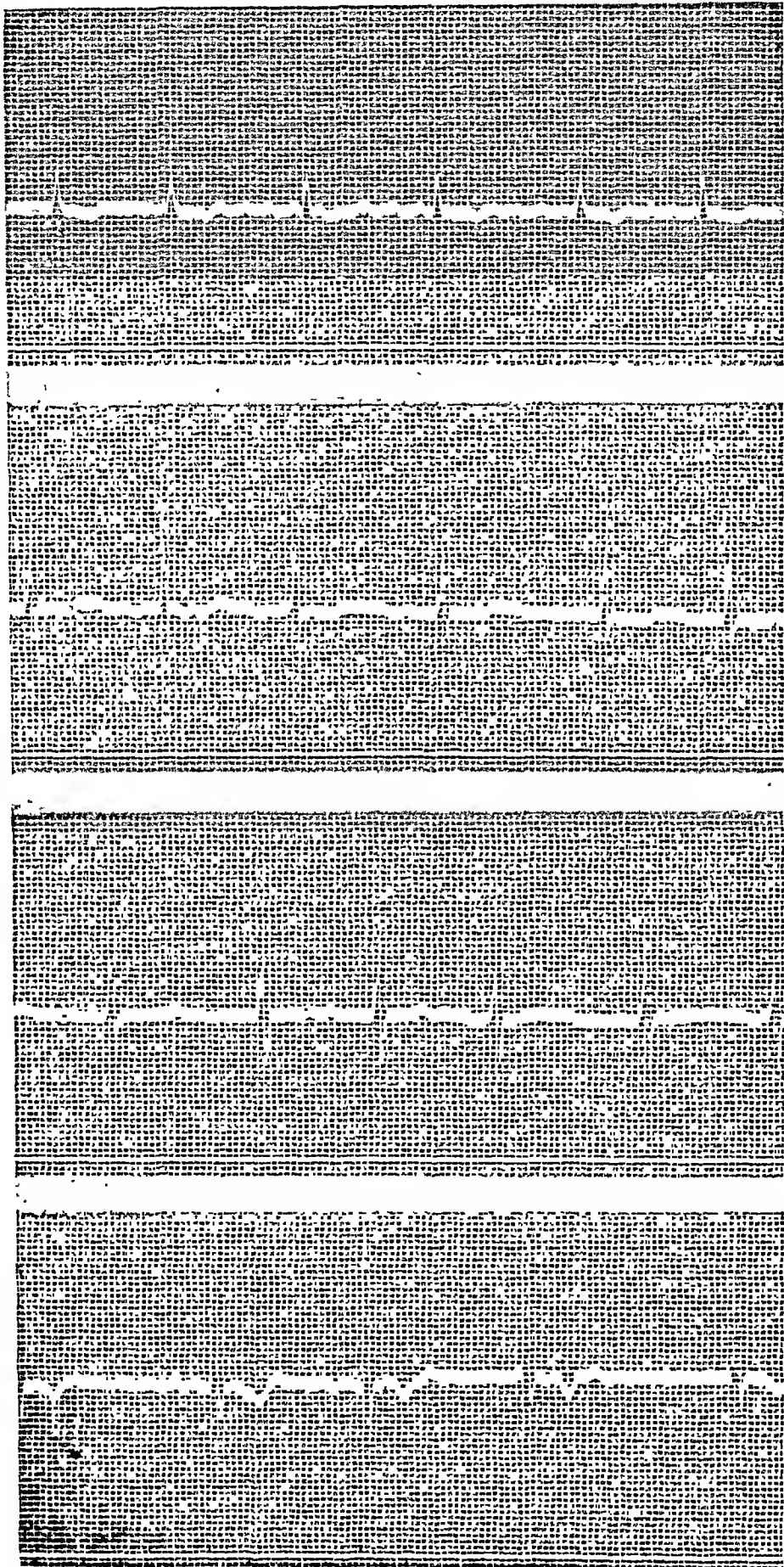


Fig. 2.—Electrocardiograms showing auricular fibrillation.

the left arm, he did quite well until his sudden death at the age of 33 years, three years after his heart first gave symptoms and 25 years after his original attack of rheumatic fever.

Autopsy.—The heart was found to be enormously enlarged, filling practically the entire chest. The heart contained over 2,000 c.c. of dark fluid blood most of which was in a massive left auricle. When opened and empty, the heart weighed 1,600 grams.

Gross Examination of Heart.—The heart was greatly enlarged and the visceral pericardium over all four chambers showed numerous loose tags of fibrous adhesions (Fig. 3). The striking feature was the size of the left auricle which was ballooned out into a large, thin sac, measuring 14 cm. in diameter. Most of the auricular wall was unusually thin and had an average thickness of 1 mm. (normal, 1 to 2 mm.), but at the top of the auricle near the auricular appendix the wall was 3 mm. in thickness (Fig. 3). The endocardium over most of the auricle was smooth and opaque, but above the posterior cusp of the mitral valve it was roughened, wrinkled, and thrown into small ridges and fissures (MacCallum's patch). On the posterior wall of the auricle there were two semilunar endocardial pockets consisting of fibrous thickening of the mural endocardium, with the concavities of these pockets pointed toward the pulmonary veins. The auricular appendix showed large and



Fig. 3.—Heart showing massive left auricle, old pericardial adhesions, and a large, curled, rubbery mitral valve without stenosis.

hypertrophied trabeculae and was free from thrombus formation. The mitral orifice was larger than normal and, before the heart was opened, must have easily admitted over three fingers. The circumference of the mitral valve measured 13 cm. (normal, 10 cm.). Both leaflets of the mitral valve were diffusely thickened, opaque, curled, and rubbery in consistency. They contained no verrucae on their closure line and no fibrous ridges indicating healing of former verrucae. There was no calcification in the mitral cusps, no predominant mitral stenosis, and no annular sclerosis. The predominant anatomic valvular lesion was a mitral insufficiency. The chordae tendineae of the mitral valve showed no shortening but were thickened and unusually long, having an average length of 3 to 4 centimeters. There was no fusion at their origin or insertion. Both papillary muscles showed slight apical fibrosis.

The left ventricle was hypertrophied and measured 2.5 cm. in thickness (normal, 1.5 cm.). The myocardium showed no visible scarring and the septum was transparent and showed no subendocardial fibrosis. The aortic orifice measured 2.5 cm. in circumference.

(normal, 7 cm.). The aortic cusps were normal and there was no verruca formation, fusion of cusps, or calcification. The orifices of both coronary arteries were normal in size. The lumen of the coronaries was patent throughout, and their intima showed only an occasional, soft, yellow plaque which did not narrow the lumen. The aortic arch was elastic, of normal thickness, and showed no atheroma with the exception of two large hyaline plaques near the orifice of the left subclavian artery. There was no syphilitic aortitis and no stenosis of the aortic isthmus. The descending aorta showed a few yellow streaks of atheroma.

The right auricle was greatly dilated and its walls were hypertrophied. The foramen ovale was closed. The right auricular appendix showed prominent trabeculation and contained no thrombus. The tricuspid orifice measured 12.5 cm. in circumference (normal, 12 cm.), and all three leaflets, while large, were normal in appearance and contained no verrucae. The chordae tendineae were delicate and not thickened.



Fig. 4.—Rheumatic, interstitial mitral valvulitis. Curled mitral leaflets without verrucae.

The right ventricle was greatly dilated and hypertrophied, especially in the pulmonary conus, and measured 8 mm. in thickness (normal, 3 mm.). The columnae carneae were hypertrophied. The pulmonic valve circumference was 8 cm. (normal). The cusps were normal and showed no verruca formation. The pulmonary artery showed no atheroma and was normal in appearance.

Anatomic Diagnosis.—The anatomic diagnosis was rheumatic heart disease with massive left auricle without mitral stenosis and chronic passive congestion of lungs, spleen, liver, and kidneys.

Histologic Examination of Heart.—The pericardium showed marked thickening due to acellular fibroblastic tissue, in which there were numerous capillaries and many areas of hyalinization. No calcification was present. The deeper portions of the visceral pericardium contained many elongated spaces lined by low cuboidal mesothelium representing remnants of the pericardial cavity isolated during the stage of active inflammation. *Diagnosis:* *healed (inactive), rheumatic pericarditis with fibrous pericardial adhesions*

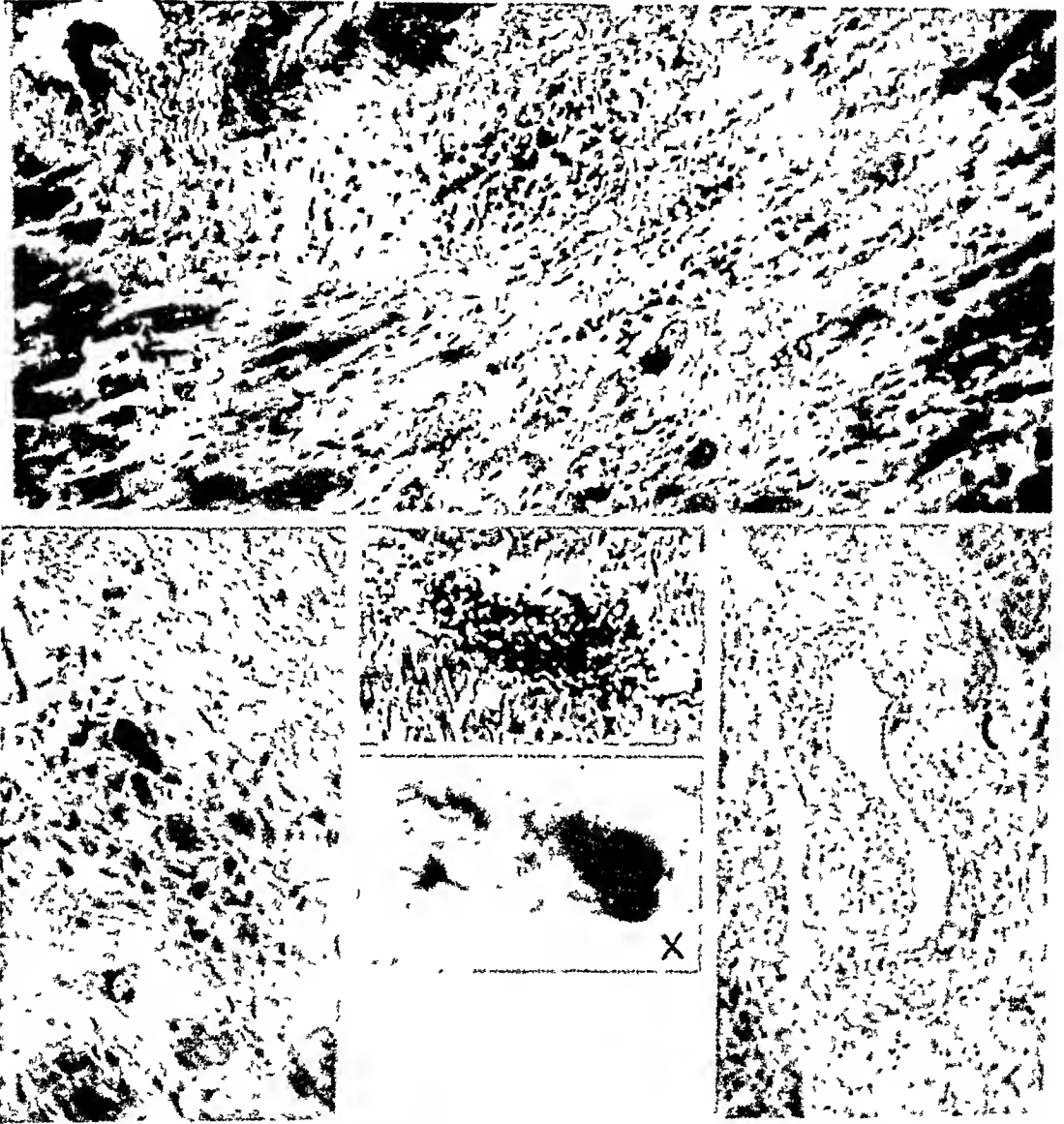


Fig. 5.—Myocardium showing hypertrophy, extensive scarring, Aschoff bodies, lymphocytic infiltration, rheumatic arteritis, and at (X) calcium deposits in individual muscle fiber.

The left ventricle showed hypertrophy. Most of the muscle fibers were increased in length and width and contained hyperchromatic nuclei with blunt ends. Many areas contained a fine acellular fibrosis between muscle bundles and even between individual fibers. A rare muscle fiber showed bluish staining of the cytoplasm suggesting calcification. The arteries in the interstitium often were surrounded by triangular acellular scars; many represented healed Aschoff nodules. Aschoff bodies in various stages of development could be found without difficulty. Numerous areas of lymphocytic infiltration occurred in the interstitial tissue near larger vessels, but there were no polymorphonuclear or eosinophilic leucocytic foci. Many of the smaller arteries showed definite endovascular thickening but

no typical arteritis verrucosa was found. *Diagnosis:* combination of *healed (inactive)* and *chronic (active)* *rheumatic myocarditis* with marked *hypertrophy*. Healing predominates.*

The mitral valve showed considerable interstitial fibrosis composed of hyalinized, acellular collagen with overlying intact but wrinkled endothelium. Arterioles were numerous at the bases of leaflets, and new capillaries extended into the cusps. No calcification was present. There was no verruca formation. Toward the central portions of the cusps numerous areas of granulomatous infiltration consisting of lymphocytes, polymorphonuclear leucocytes, and a few eosinophiles were seen. *Diagnosis:* *healed (inactive)* and *chronic (active)* *rheumatic valvulitis* with inactive lesions predominating.*

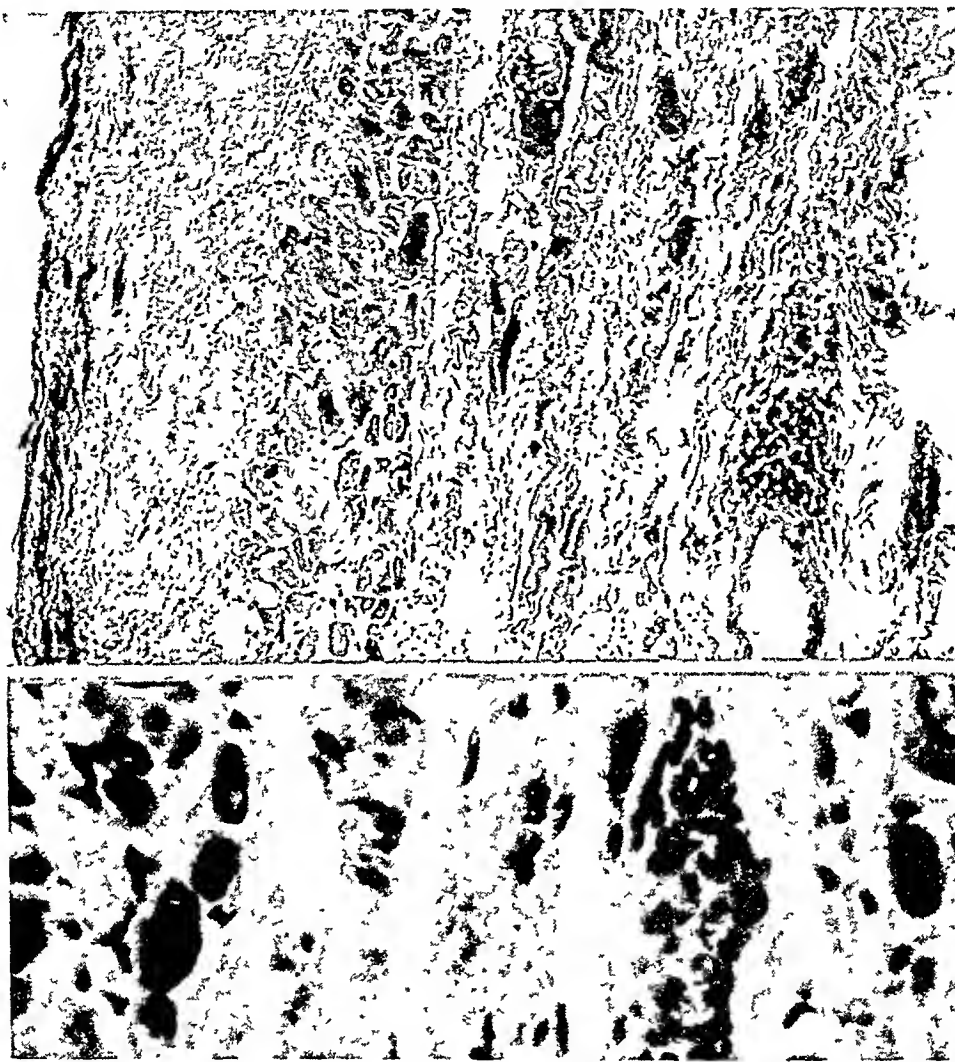


Fig. 6.—Left auricle showing extensive rheumatic auriculitis. Marked muscle atrophy, necrosis, fibrosis, and cellular infiltration may be noted.

The left auricle was the seat of the most extensive damage. Most of the auricular wall was thinner than normal due to marked muscle atrophy. The endocardium was intact, with an occasional histiocyte. There was marked thickening of the subendocardium due to great increase in acellular connective tissue. Between the subendocardium and the muscularis, atypical Aschoff bodies were easily recognized, consisting of cells with sharply defined nuclei with basophilic cytoplasm.

The muscularis showed great damage. Areas of muscle necrosis without much inflammatory reaction were frequent. This resulted in isolated, greatly hypertrophied muscle fibers with large, hyperchromatic nuclei. The adventitia showed marked perivascular lymphocytic

*The terminology used here conforms to that of the Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, New York, 1940.

infiltration and many of the smaller arteries showed marked endarteritis with thickened walls. Polymorphonuclear leucocytic foci were infrequent. The thicker parts of the auricular wall near the appendix showed muscle tissue, well preserved with an occasional area of calcification. *Diagnosis:* combination of *healed (inactive)* and *acute rheumatic auriculitis*, involving most of the auricular muscle and producing marked dilatation and thinning of the auricle.*

The aorta showed no definite rheumatic lesions. There were occasional subintimal lipoidal deposits. The adventitia was normal and free from lymphocytes.

The lungs, spleen, and liver showed only chronic passive congestion.

DISCUSSION

Mode of Production of Massive Left Auricle in Case Reported.—Examination of the heart leaves no doubt that death was due to severe rheumatic heart disease in various stages of activity and healing. Since there was no evidence of predominant mitral stenosis, the massive left auricle can be best explained on a mechanical basis somewhat similar to that which occurs in muscular insufficiency of the mitral valve. Mitral insufficiency without an accompanying stenosis is a rather unusual lesion in rheumatic heart disease. Osler¹⁹ stated that, "Except in children, we rarely see the mitral leaflets curled and puckered without narrowing of the orifice."

We are of the opinion, therefore, that the chronological events in this case were somewhat as follows:

1. Rheumatic valvulitis of the mitral valve and at the same time or soon after a rheumatic carditis initiated the development of the lesion.

2. As a result of this inflammation the muscle of the left ventricle was weakened and a certain amount of dilatation occurred. The rheumatic process also produced an interstitial valvulitis of the mitral valve. This involvement did not produce stenosis, verrucae, shortening and fusion of chordae tendineae, fusion of the cusps, or calcification. It did, however, produce rubbery, curled, and puckered leaflets. This deformity of the leaflets together with the marked dilatation of the mitral ring resulted in improper closure of the valve and mitral insufficiency. The subsequent developments followed the course which was clearly described by Osler.¹⁹

3. The imperfect closure of the mitral valve allows a certain amount of blood to regurgitate from the ventricle into the left auricle so that at the end of auricular diastole this chamber contains not only blood which it has received from the lungs, but also that regurgitated from the left ventricle. This necessitates dilatation and, as increased work is thrown upon it in expelling the augmented contents, hypertrophy of the left auricle.

4. With each systole of the left auricle a larger volume of blood is forced into the left ventricle, causing a certain amount of dilatation and hypertrophy (the left ventricle does not hypertrophy normally in mitral stenosis unless there are lesions on the aortic valve).

5. During the diastole of the left auricle, as blood is regurgitated into it from the left ventricle, the pulmonary veins are less readily emptied. In consequence the right ventricle expels its contents less freely and in turn becomes hypertrophied and dilated.

6. Finally, the right auricle also is involved. Its chamber enlarges and its walls increase in thickness.

7. In this case which we are discussing, this whole sequence of events was made much worse by the extensive auriculitis in the left auricle which shows rheumatic lesions of greater severity than any other part of the heart. Once dilatation of the left auricle began, the condition of this chamber became progressively worse until it finally became an enormous sac possessing very little contractility.

This result was undoubtedly contributed to by undue physical exercise between the ages of 15 and 20 years.

It is astonishing how long such a patient may live before congestive failure sets in, but the whole sequence of events is slow and compensation is maintained by hypertrophy of both ventricles.

Previous Explanations of Massive Left Auricle.—Most authorities agree that massive left auricle is unusual and that its development depends on the following factors: that because of its thin walls the left auricle is more capable of dilatation than the other chambers of the heart; that the left auricle has no safety valves such as the great veins give the right auricle; that whenever mitral disease is present the left auricle is bound to be filled by both ventricles since even with mitral stenosis there is combined insufficiency; and that any lesion or disease capable of causing increased left auricular pressure can be the underlying factor in the production of massive left auricle.²⁻¹⁵

The literature, however, often fails to give a clear conception of the cardiac pathology associated with massive left auricle, the predominant lesion of the mitral valve, whether stenosis or insufficiency, and the condition of the auricular wall.

Rheumatic heart disease is considered by most observers as the type of disease in which most of these enormous left auricles occur. Many reports, however, fail to show which portions of the heart are most affected and whether active rheumatic lesions are present.

Causes other than valvular disease have been cited in a few cases. Peel,¹⁷ observed marked dilatation of both auricles in a case showing no valvular disease and considered it as secondary to heart block. Dialer¹⁸ showed that tuberculous fibrosis of the auricular musculature might result in massive left auricle.

Mitral stenosis is assumed by most authorities to be the main factor in the production of massive left auricle. There is no doubt that tight mitral stenosis, such as occurs in chronic valvular defects due to rheumatism or localized arteriosclerosis, is often followed by hypertrophy and dilatation of the left auricle. The auricle may reach a considerable size. White²⁰ states that in mitral stenosis "the left auricle, being affected first, may assume enormous proportions; and cases are on record in which its bulk was larger than that of all the rest of the heart, its capacity increasing even to 1,000 c.c. or more (normal about 125 c.c.)." If this is true, some of these auricles have reached a size sufficient to be regarded as "massive." However, in over 15,000 autopsies by one of us (H. S. M.), we have never encountered predominating mitral stenosis which produced really massive left auricles.

In the cases reported by Owen and Fenton,¹ Emanuel,² and Bach and Keith,¹⁵ there was no mitral stenosis but only dilatation of the mitral valve. In a case reported by Bishop and Babey,¹³ in which the left auricle was 12 cm. in diameter and held 1,550 c.c. of water, there was a rheumatic mitral valvulitis with only a small degree of mitral stenosis. The mitral valve measured 9 cm. in circumference. Microscopic examination of the left auricle "was characterized by a marked thinning of the muscle layer, the myocardium occupying but a small proportion of the entire thickness."

There is therefore considerable evidence in the literature to support our contention that predominant mitral stenosis is not a factor in the production of these enormous left auricles. If it were, massive left auricle would be more frequently encountered.

Fibrosis of the left auricle has been mentioned in only a few cases as one of the most important factors in the production of massive left auricle. Most reports do not specifically mention the predominance of rheumatic lesions in the left auricular wall and the presence of a rheumatic auriculitis. Bramwell and Duguid,¹⁰ and later Nichols and Ostrum,¹² first suggested that in massive left auricle there was more evidence of rheumatic myocarditis with fibrosis in the left auricle than in any other part of the heart. Once the left auricle becomes fibrotic, it is only necessary that the left ventricle be competent and capable of exerting a sufficient back pressure and the auricle will then begin to dilate.

Clinical Features.—The symptoms and findings in our cases are more or less typical of the entire group. Most of the massive left auricles occur in rheumatic heart disease. Various murmurs are heard and varying amounts of dullness on percussion of the cardiac outline are present depending on the degree of auricular enlargement. Pain in the chest is common, more often on the right side. Difficulty and pain on swallowing are frequent, due to pressure and distortion of the esophagus by the large auricle. A dry, non-productive cough is common.

Auricular fibrillation, though it is not always present, is very common. It is probably the result of the great amount of auricular damage due both to the rheumatic auriculitis and the great expanse of the auricular wall.

When the heart becomes large enough, heart sounds will be heard in the right axillary line as well as over the rest of the chest. Other symptoms will appear as failure or other complications occur.

The fluoroscopic and x-ray findings are characteristic. It is in the postero-anterior view that massive left auricle is usually recognized. As the heart is observed under the fluoroscope or viewed in x-ray films, there is on the right side of the heart a more dense shadow, to the right of which there is a less dense one; the so-called "double contour shadow." The dense shadow is the right auricle with the left auricle lying to the right of this portion of the heart. When the enlargement of the left auricle is not quite so great, the right border of the heart shadow looks like a double convex curve, with one arc above the other. The upper arc is the left auricle and the lower one is the right. In the right anterior oblique position, the enlarged left auricle of

rheumatic heart disease encroaches upon the mid-portion of the retrocardiac space. However, in these massive hearts there is more and more encroachment upon this space as the auricle enlarges. When the patient is given barium paste, the esophagus is readily seen pushed backward and to the right by the massive left auricle. There is usually delay in the passage of the barium.

Why the left auricle should appear on the right side of the heart is a controversial subject. Nichols and Ostrum¹² suggest that whenever the left auricle becomes enlarged there is also enlargement of the right auricle, thereby causing a rotation of the entire heart to the left. This results in the left auricle swinging to the right of its normal position. Since the left auricle cannot then enlarge to the left because it is unable to expand through the arch of the aorta, and since the spine blocks it from behind, the left auricle can only enlarge to the right, forward, and upward, producing the unusual picture seen in massive left auricle.

Steele and Paterson²¹ have a slightly different concept to offer. They state that the anatomic position of the left auricle is normally uppermost and posterior. The tracheal bifurcation is just above it with the left main bronchus resting upon it and the esophagus passing right behind it. Therefore, because of its posterior position and anatomic borders, this part of the heart may enlarge either to the left or to the right. However, because of the fixed structures about it, once it gets beyond a certain point, the enlargement must of necessity be to the right.

One of the most interesting clinical aspects of massive left auricle is the remarkable physical capacity of these patients in spite of the tremendous cardiac enlargement. It has been suggested,¹⁰⁻¹² that the main positive factor in this cardiac reserve lies in the integrity of the heart muscle other than the left auricle. As a result, the ventricles are able to do their job in an adequate fashion as long as the auricles keep supplying them with blood. In these cases, because of the huge capacity of the enlarged left auricle, enough blood usually does get into the left ventricle in spite of the fact that the auricular contractions are poor and because there is no predominant mitral stenosis.

SUMMARY

1. Three main factors seem to be essential for the formation of most cases of massive left auricle: (a) *rheumatic carditis* over a long period of time, showing various phases of activity with predominant inactivity and healing during the last few years of life; (b) *mitral insufficiency* due to rheumatic myocarditis of the left ventricle in various stages of activity and healing and rheumatic valvulitis characterized by curled and rubbery mitral segments (in our experience, predominating mitral stenosis will not produce such massive auricles); and (c) *rheumatic auriculitis* in various stages of activity and healing with marked muscular atrophy and fibrosis, of such intensity that the left auricle is often more severely damaged than any other part of the heart.

2. The importance of an undue amount of physical exercise during the early stages of rheumatic heart disease, such as this patient indulged in, must

be stressed as a contributory factor in overdistention of the diseased left auricle.

3. Massive left auricle is perhaps not as unusual as we are led to believe. It has been observed in induction centers in men who have enormous hearts and who are in a fair state of health. It is characteristic of the lesion that individuals can be comfortable with no cardiac symptoms for a period of years before decompensation sets in.

4. It would seem that too much importance is placed by cardiologists on so-called "Combined Lésions" of the valves. In the case of the mitral valve it is widely held "that all stenotic valves have some regurgitation and all insufficiencies have some degree of stenosis." This concept seems to have developed in order to explain the presence of certain murmurs, often of little consequence. It has led to considerable confusion. Certainly at autopsy it is comparatively simple to determine whether stenosis or insufficiency predominates; it is also simple to determine that the various dilatations and hypertrophies due to valvular defects depend chiefly on the predominating lesion.

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THE EFFECT OF CERTAIN DRUGS UPON THE CARDIOTOXIC LESIONS OF DIGITALIS IN THE DOG

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IN A recent editorial in *The Journal of The American Medical Association*,¹ attention was drawn to the fact that digitalis preparations are capable of producing, among other toxic effects, myocardial lesions in experimental animals. This effect of digitalis has been described in many publications, the most noteworthy of which were contributed by Buchner,² Hu, Lieu, and Li,³ La Due,⁴ and by Dearing, Barnes, and Essex.⁵ In all reports, the cardiac changes resulting from digitalis administration have been similar. The lesions consist of areas of focal necrosis, fraying of the muscle fibers, fibrosis, hemorrhages, and cellular infiltrations.

Our interest in this work was stimulated by the fact that these pathologic changes are almost identical with those produced in dogs by Manning, Hall, and Banting⁶ as a result of vagal stimulation, and by Hall and his associates⁷ as a result of injections of acetylcholine iodide.

Since no evidence has been submitted as to the mechanism of how digitalis preparations are capable of producing myocardial lesions, our efforts have been made in an attempt to shed some light upon this problem.

PROCEDURE

Thirty-two young dogs were studied in this experiment. Seven animals received 2 or 3 cat units of digiglusin daily, depending upon the dog's tolerance to the drug. Five animals were given digiglusin plus $3\frac{3}{4}$ grains of aminophylline twice daily. Five dogs received digiglusin plus 3 grains of theobromine sodium acetate three times daily. Eight dogs were given injections of digiglusin plus $1\frac{1}{2}$ grains of papaverine hydrochloride twice daily. Seven animals were treated with digiglusin and atropine sulfate. The latter drug was administered by mouth in tablets of $\frac{1}{75}$ grain four times daily and in addition all water was atropinized with $\frac{1}{65}$ grain to the liter. All animals were observed daily, and, when it was obvious that death was imminent, the dog was given an ether anesthetic and the heart was removed. Blocks of tissue were taken from the right and left auricles, anterior left ventricular wall, posterior left ventricular wall, lateral wall of the left ventricle, anterior right ventricular wall, posterior right ventricular wall, and the interventricular septum. Tissue was fixed in formalin and sections were made and stained with hematoxylin and eosin.

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RESULTS

All animals receiving injections of digiglusin alone developed microscopic myocardial changes. These consisted of areas of vacuolation of cells, focal necrosis and hyalinization, round cell and polymorphonuclear infiltrations, hemorrhages, and fibroblastic proliferation. These lesions are similar to those described by previous investigators.

The dogs receiving aminophylline and digiglusin developed only minimal and scattered lesions consisting of slight edema and loss of striations of the muscle fibers. Theobromine sodium acetate with digiglusin was admin-

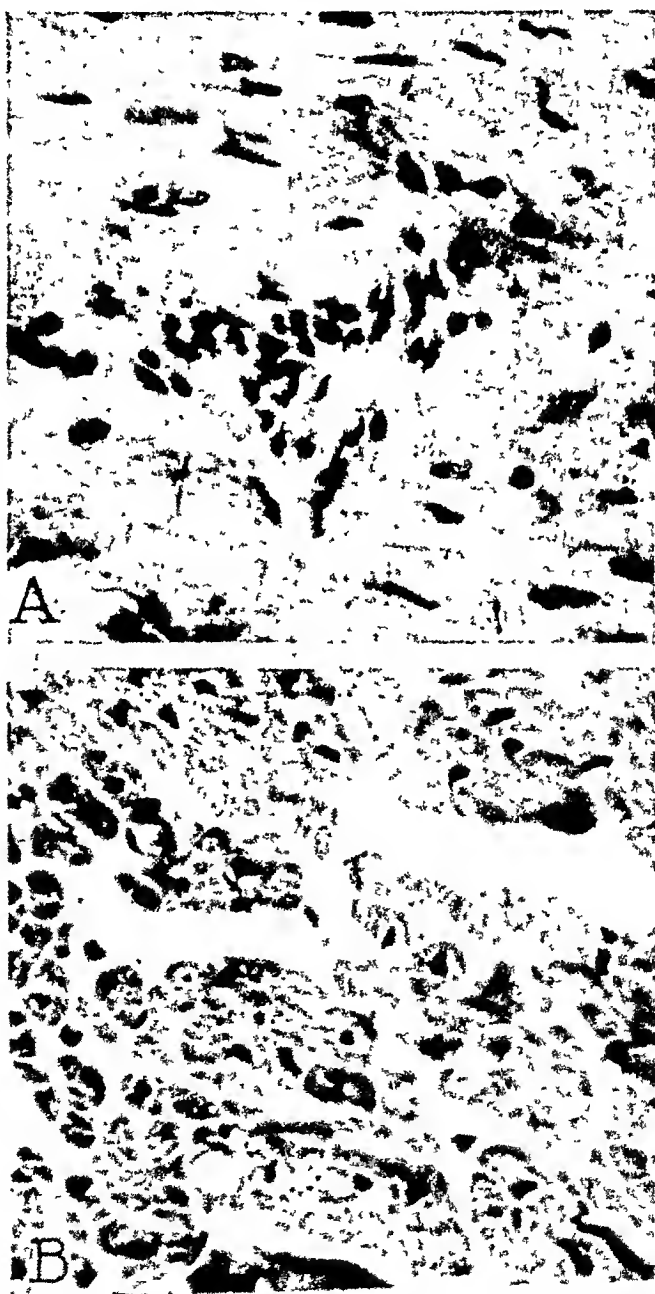


FIG. 1.—A, Dog 4. Digiglusin alone. Round cell infiltration ($\times 500$). B, Dog 2. Digiglusin alone. Vacuolation and necrosis of cells ($\times 500$).

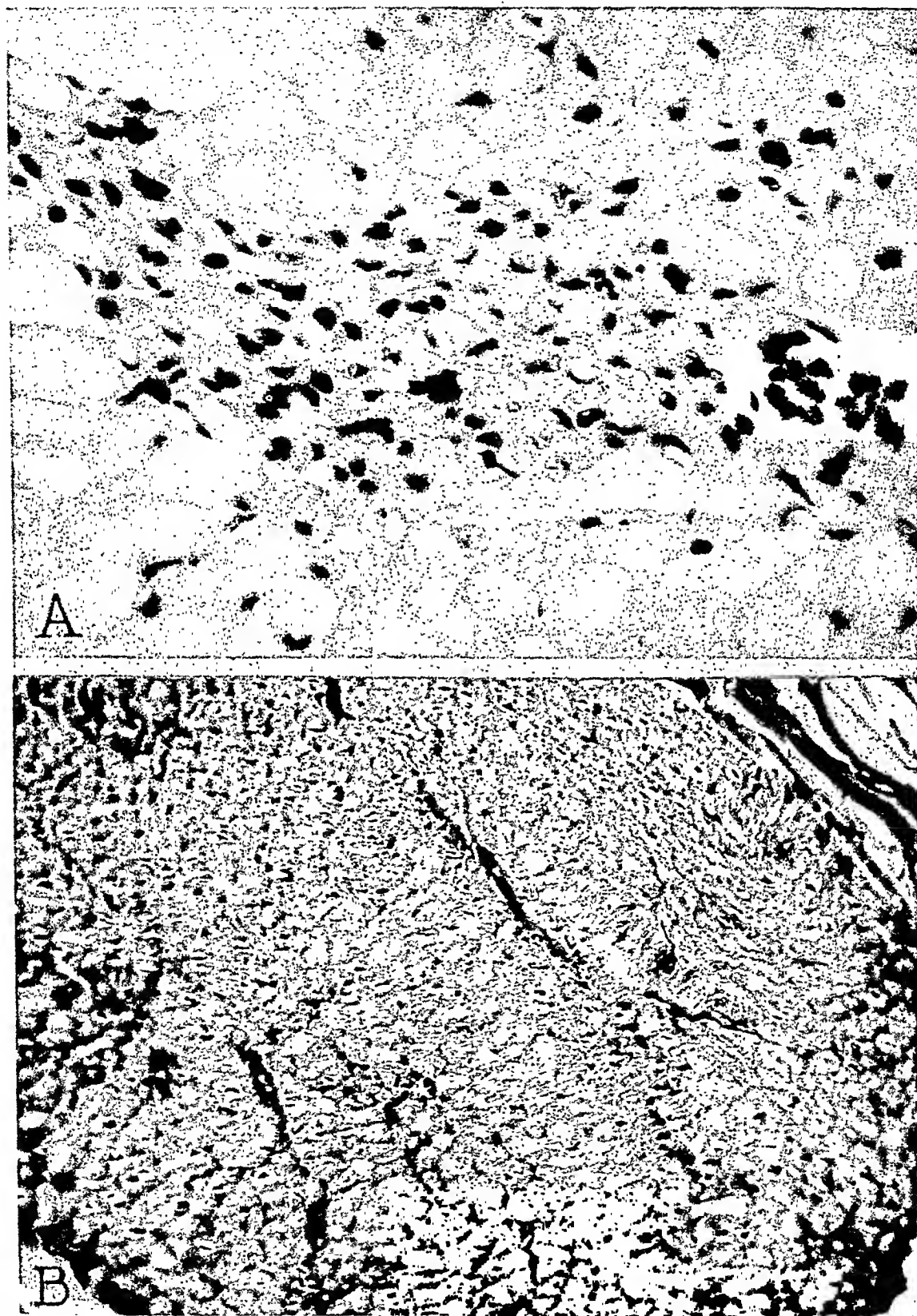


Fig. 2.—A, Dog 3. Diglugin alone. Proliferation of fibroblasts ($\times 800$). B, Vacuolation of cells ($\times 275$).

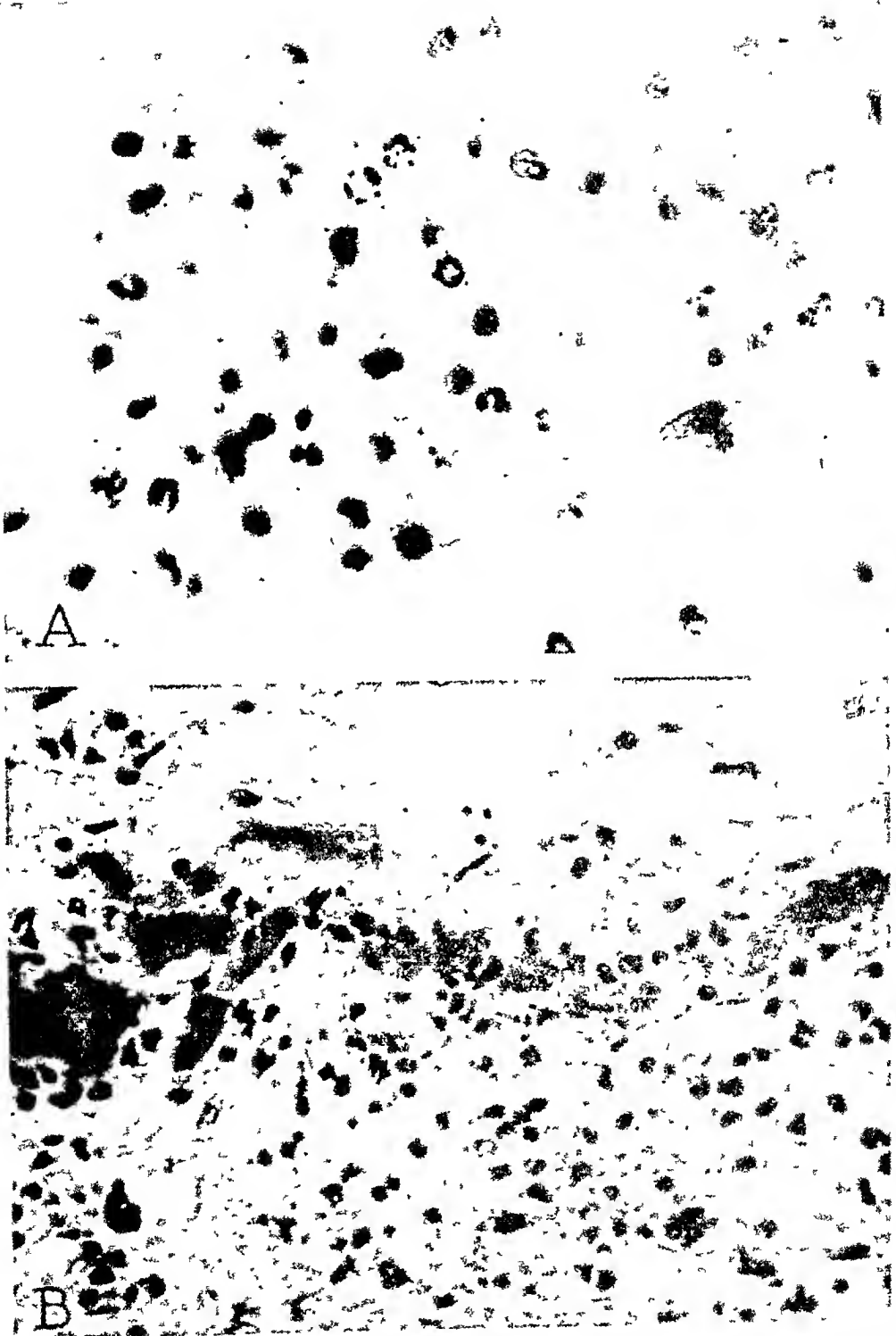


Fig. 3-1. Fig. 30. Distribution plus character. Necrosis of cells with lymphocytic infiltration (A). Fig. 30. Necrosis of cells with lymphocytic infiltration (B).

istered to five dogs. Three of these animals developed minor changes made up of occasional areas of vacuolation and polymorphonuclear infiltration. Two of the dogs that received theobromine had lesions equally as marked as those that received digiglusin alone.

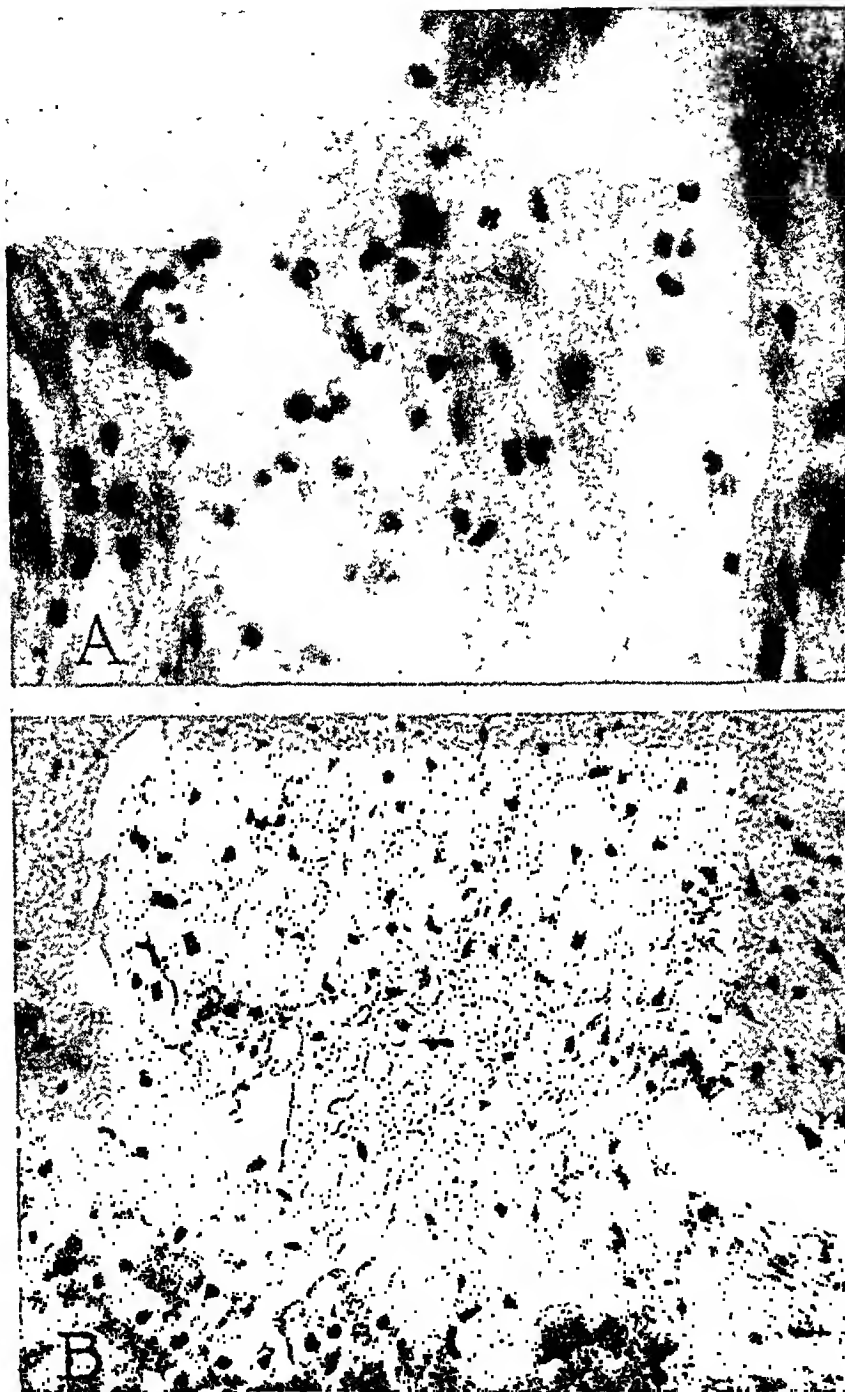


Fig. 4.—A, Dog 423. Digiglusin and papaverine. Polymorphonuclear and round cell infiltration ($\times 660$). B, Dog 405. Digiglusin and papaverine. Vacuolation of cells ($\times 470$).

Papaverine hydrochloride with digiglusin was injected into eight animals, seven of which revealed very marked myocardial abnormalities identical with those that were found in the animals receiving only digiglusin.

TABLE I. DATA OF DOGS RECEIVING ONLY DIGIGLUSIN

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
1	February 10 to May 6 86 days	144	Heart slightly dilated	Hemorrhage into muscle, mild hyalinization of fibers, fraying of fibers
2	February 10 to April 26 76 days	96	Normal heart	Round cell accumulations, hyalinization of fibers, vacuolation of fibers, loss of striations in fibers, fraying of fibers
3	May 28 to July 2 34 days	88	Heart mildly dilated	One area suggestive of infarction with fibroblasts, polymorphonuclear leucocytes, and necrosis. Vacuolation of fibers. Hemorrhages, highly cellular scar
4	June 28 to August 17 51 days	110	Heart mildly dilated	Scattered areas of polymorphonuclear leucocytes. Foci of lymphocytes, loss of striations of muscle fibers, edema of fibers
5	June 28 to August 20 54 days	119	Heart mildly dilated	Necrosis of fibers, hyalinization of fibers, edema, round cell infiltration
6	October 27 to November 23 28 days	67	Heart mildly dilated	Vacuolation of fibers, edema
7	October 27 to November 17 21 days	52	Normal heart	Necrosis of fibers, one small area of fibrosis, hemorrhages, small accumulation of polymorphonuclear leucocytes

TABLE II. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS AMINOPHYLLINE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
8	October 27 to November 22 27 days	64	Heart mildly dilated	Slight loss of striations in fibers. Congestion of vessels
9	October 27 to December 2 37 days	88	Heart mildly dilated	Normal myocardium except for a few pyknotic nuclei
441	January 17 to February 5 20 days	36	Normal	Normal myocardium. Venous congestion
444	January 17 to February 2 17 days	29	Normal	One area in which fibers were separated by fibrous tissue
449	February 3 to February 23 20 days	40	Normal	Slight edema of fibers. Distention of veins

Two of the atropinized animals developed definite cardiac changes. However, five dogs had hearts with only occasional areas of cellular infiltration and slight vacuolation of muscle fibers. The degree of these changes was much less than those in the animals receiving only digiglusin.

All data for the entire experiment are summarized in Tables I to V.

Figs. 1 to 4 are photomicrographs showing the pathologic changes described.

TABLE III. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS THEOBROMINE SODIUM ACETATE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (G.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
425	February 6 to March 7 29 days	61	Normal heart	Occasional area of polymorphonuclear infiltration, vacuolation, and fibroblastic proliferation
428	February 6 to March 7 29 days	61	Normal heart	Hemorrhage, polymorphonuclear infiltrations, vacuolation
430	February 6 to February 23 17 days	30	Normal heart	One area of polymorphonuclear infiltration
431	February 6 to March 9 31 days	64	Normal heart	One area of vacuolation and cellular infiltration
432	February 6 to March 9 31 days	64	Normal heart	Slight vacuolation

TABLE IV. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS PAPAVERINE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (G.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
404	September 25 to October 20 26 days	45	Normal	Areas of hemorrhage into muscle and areas of vacuolation
405	September 25 to November 10 47 days	90	Normal	Cloudy swelling, vacuolation of fibers, hemorrhages, few areas of polymorphonuclear infiltration
460	September 25 to November 14 51 days	100	Normal	Vacuolation, polymorphonuclear infiltration, hemorrhages into fibers, round cell infiltration
423	October 6 to November 29 55 days	114	Normal	Hemorrhages, polymorphonuclear infiltration, round cell infiltration
406	October 12 to November 29 49 days	102	Normal	Polymorphonuclear infiltration, round cell infiltration, areas of vacuolation
455	January 17 to February 12 27 days	53	Normal	Slight edema of fibers
437	February 9 to March 4 25 days	50	Normal	Vacuolation of fibers, necrosis, collections of round cells
10	October 27 to November 22 27 days	64	Mildly dilated	Marked necrosis, round cell infiltration hemorrhages

DISCUSSION

If, by experimental investigation, the mechanism of action of certain drugs can be more clearly elucidated, a definite contribution will have been made which will be of value both to the research worker and to the practicing physician. All of the preparations used in this study are frequently used in clinical medicine and, for this reason, the conclusions reached should be of definite value to those interested in treating heart disease.

It is obvious from the results of this study that certain drugs are capable of minimizing the cardiotoxic effects of digitalis. This fact gives a clue as to

TABLE V. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS ATROPINE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (c.c.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
401	September 25 to November 14 51 days	98	Normal	One small area of vacuolation
418	October 6 to November 10 36 days	66	Normal	Vacuolation of fibers, round cell infiltration, polymorphonuclear infiltration
414	October 12 to November 29 50 days	105	Normal	Vacuolation of fibers, hemorrhages, polymorphonuclear and round cell infiltration
415	October 7 to November 24 48 days	112	Normal	Occasional polymorphonuclear accumulation. One small area of vacuolation
412	September 29 to November 24 57 days	120	Normal	Few areas of vacuolation, occasional areas of polymorphonuclear infiltration
462	February 24 to March 24 30 days	66	Normal	One small accumulation of round cells
438	January 17 to February 12 27 days	56	Normal	Few collections of round cells, slight vacuolation of fibers

the mechanism by which digitalis preparations are able to produce myocardial lesions. This harmful action of digitalis can be mediated in one of three ways: (1) by direct action of digitalis upon the myocardium; (2) by stimulation of the vagus nerve resulting in the liberation of acetylcholine, which substance produces coronary vasoconstriction; or (3) by a direct action upon the coronary arteries resulting in constriction of these vessels.

If the myocardium is injured through the first or third mode of action, then all of the animals in this experiment should have developed myocardial changes because all dogs received digiglusin. This did not occur and we therefore feel that the toxic action of digitalis is not a direct one.

Since atropine sulfate definitely minimized the cardiac changes which occurred, we feel justified in presenting the following hypotheses: (1) The cardiotoxic effect of digitalis in the dog is the result of vagal stimulation, which produces coronary constriction resulting in myocardial ischemia. (2) This specific result of digitalis administration may be modified by administering a drug which will overcome or prevent coronary artery constriction. In this work aminophylline, theobromine sodium acetate, and atropine sulfate were drugs which had this action. The former was the most efficient.

A rather surprising result of this work is the evidence that papaverine did not modify the effect of digitalis. Since the xanthine drugs were used in dosages which are usually employed clinically, it was felt that $1\frac{1}{2}$ grains of papaverine hydrochloride given twice daily would be adequate for purposes of comparison. We have found no evidence in our experiments that indicates why papaverine was ineffective. Richards,* in some unpublished work, has evidence that the vasodilating effect of papaverine is very transient compared with that of aminophylline. This may explain the results we have obtained. It is also

possible that we did not use an adequate dose of papaverine. We feel, however, that in evaluating one drug with another comparative quantities must be used. It would seem unfair to compare the effect of papaverine with aminophylline if the usual clinical dose of aminophylline was evaluated against twice the clinical dose of papaverine. Further work on the vasodilating action of papaverine is now in progress, in which larger doses of this drug are being employed.

Theobromine sodium acetate is, in our opinion, more effective in effecting an increase in the coronary flow than is aminophylline. It is probable that giving the drug by mouth made some difference and that this also influenced the effect of the atropine.

SUMMARY

An experiment is presented in which it is shown that the cardiotoxic effects of digitalis in the dog may be modified by the use of aminophylline, theobromine sodium acetate, and atropine sulfate. Papaverine hydrochloride did not minimize the cardiac changes produced by digitalis administration.

A theory is discussed which could explain the results of this study.

CONCLUSIONS

1. Digitalis in toxic doses produces myocardial lesions in the dog.
2. Aminophylline and theobromine sodium acetate in doses usually employed clinically are capable of modifying this toxic effect of digitalis.
3. Aminophylline was more efficient than theobromine in preventing the myocardial lesions resulting from the administration of digitalis.
4. Atropine sulfate is capable of ameliorating the cardiotoxic effect of digitalis.
5. Papaverine hydrochloride, in the usual clinical dose, did not prevent the cardiac changes produced by the administration of digitalis.

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THROMBOPLASTIC PROPERTIES OF SOME MERCURIAL DIURETICS

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IN A PAPER read at a meeting of the American Medical Association in 1942, the present writer announced a pharmacologic discovery, which in the past three years has been followed by developments of considerable clinical importance.¹ It is for this reason that the present preliminary announcement is being published. At the A.M.A. meeting it was reported that, when repeated samples of blood are taken from cats during intravenous injections of digitalis or ouabain solutions for purposes of assay, the coagulation time of the blood samples as determined by Howell's method progressively shortens. This phenomenon did not occur in control experiments. The same phenomenon of marked decrease in coagulation time was observed following the administration of digitalis to rabbits, when the blood samples were obtained by direct heart puncture. This thromboplastic effect was also produced *in vitro*, not only by digitalis and ouabain, but also by all digitaloid glucosides which we were able to obtain. Numerous other drugs were used as controls. With but few exceptions these drugs did not bring about a decrease in coagulation time; the most outstanding exception was epinephrine. These findings were corroborated by Werh² on rabbits; and still further by de Takats, Trump, and Gilbert.³ The latter authors stressed the clinical significance of the phenomenon, because they regarded it as the most plausible explanation of sudden death in patients under digitalis therapy, who unexpectedly develop thromboembolic accidents. Recently these findings have been still further corroborated.⁴

In 1943, the author amplified his original findings in a report made before a joint meeting of the American Therapeutic Society⁵ and the Southern Medical Association⁶ and ventured to predict that other drugs might exhibit similar thromboplastic properties, which might precipitate thromboembolic complications. The author has already found this to be the case with intravenous injections of cobra venom and of Congo red.⁷

The prediction mentioned has been brilliantly confirmed by the report made in 1945 by Moldavsky, Hasselbrock, Cateno, and Goodwin, who found that varying dosages of penicillin administered by both the oral and intramuscular routes, "produced a marked increase in the speed with which the blood clotted in human patients."⁸

For this reason, in the interest of preventive medicine and public health, the present writer wishes to announce his studies on another important group of drugs extensively employed in therapeutics. In the fall of 1943, experiments

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were begun on rabbits and cats, and to a lesser extent on dogs, concerning the thromboplastic properties of certain mercurial diuretics widely employed in cardiovascular practice. The three diuretics studied were Mercupurin, Salyrgan, and Mercuhydrin. Inasmuch as Mercupurin* and Salyrgan* are marketed in combination with theophylline, experiments were performed not only with such commercial solutions, but especially with solutions of the mercurials without theophylline.

It was found that all three of these mercury compounds, both by intramuscular injection and by injection into a vein, exerted a definite thromboplastic effect on the blood of rabbits and cats. Such an effect usually developed one to two hours after administration of the drugs but sometimes appeared much earlier. Numerous control experiments with other drugs, including caffeine, diuretin, theophylline, aminophylline, and sulfadiazine, did not indicate that these drugs produced an increase in the speed of clotting. Penicillin was used in control experiments and produced a marked thromboplastic effect, thus corroborating the findings of Moldavsky and his co-workers.

Eighty experiments on rabbits, and thirty-five on cats have already been performed in studying the thromboplastic property of mercurials. The following protocols will serve as illustrations of the results which will be published in detail later.

On June 27, 1945, a brown rabbit weighing 2,000 grams received 10 mg. of Mercupurin intravenously. The coagulation time before injection of the mercurial was 7 minutes. One hour after injection of the mercurial, the coagulation time was 4 minutes. Three hours after the injection the coagulation time was $3\frac{1}{2}$ minutes.

On June 27, 1945, a white rabbit weighing 2,000 grams was given 10 mg. of Salyrgan into an ear vein. The coagulation time before the mercurial was injected was 12 minutes. One hour after injection the coagulation time was $4\frac{1}{2}$ minutes. Two and one-half hours after the injection of the mercurial, the coagulation time was 4 minutes.

On June 1, 1945, a grey rabbit weighing 1,800 grams received 0.5 c.c. of Mercuhydrin solution intravenously. The coagulation time before injection was 7 minutes. Forty minutes after injection the coagulation time was $1\frac{1}{2}$ minutes. One and one-half hours after injection, the coagulation time was $2\frac{1}{2}$ minutes. Three hours after injection the coagulation time was $3\frac{1}{2}$ minutes.

On June 11, 1945, a white rabbit weighing 2,200 grams received 20 mg. of Mercupurin intramuscularly. The coagulation time before the injection was found to be $9\frac{1}{2}$ minutes by seven determinations on two successive days. Two hours after the mercurial was injected the coagulation time was $3\frac{1}{2}$ minutes.

On June 11, 1945, a grey rabbit weighing 2,100 grams was given 20 mg. of Salyrgan intramuscularly. Seven determinations on two successive days showed the coagulation time to be $7\frac{1}{2}$ minutes before the mercurial was administered. Two hours after the mercurial the coagulation time was $1\frac{1}{2}$ minutes. Three hours after injection the coagulation time was 4 minutes. On the following day, the coagulation time was 7 minutes.

On June 15, 1945, a grey rabbit, weighing 2,000 grams received 10 mg. of Mercuhydrin intramuscularly. The coagulation time before the injection was 7 minutes. Thirty minutes after the injection the coagulation time was still 7 minutes. Three hours after the injection the coagulation time was $2\frac{1}{2}$ minutes.

On June 8, 1945, a small cat weighing 1,000 grams was anesthetized with Nembutal and given Mercupurin intramuscularly. The coagulation time before the injection of the

*These preparations were furnished through the courtesy of the manufacturers, The Campbell Products, Inc., supplying Mercupurin and The Winthrop Chemical Co., Inc., Salyrgan.

mercurial was 13 minutes. Twenty-four minutes after the injection, the coagulation time was 12 minutes. One hour after the injection, the coagulation time was 1 minute. One and one-half hours after the injection of mercurial the coagulation time was $2\frac{1}{2}$ minutes. Three hours after the injection the coagulation time was 4 minutes.

On June 8, 1945, a small cat, weighing 900 grams, received 10 mg. of Salyrgan intramuscularly. The coagulation times were $6\frac{1}{2}$ minutes before injection; 1 minute, fifty-five minutes after injection; and 2 minutes, 45 seconds, two hours after the injection.

On June 1, 1945, a rabbit weighing 2,000 grams was used as a control. It received 10 mg. of theophylline intravenously. The coagulation times were $11\frac{1}{2}$ minutes before the injection; $10\frac{1}{2}$ minutes, one hour after the injection; 11 minutes, two hours after injection; 11 minutes, three hours after injection; and 12 minutes, three and one-half hours after injection.

COMMENT

In the present paper the results obtained with the clotting of whole blood only are reported. The phenomenon of clotting is, of course, a very complex one. The exact mechanism in any given case involves a study of platelets and determinations of prothrombin, of calcium, of fibrinogen, of antibodies, and of those other clotting factors in the blood which, as Theis⁹ put it, "as yet, cannot be effectively measured." Such studies are now in progress and will be reported. It may be added that the three mercurial diuretics which we particularly studied were not the only ones which increased the speed of clotting; a number of other mercury compounds also exhibited this property.

Sudden death from mercurial diuretics has been repeatedly described and a valuable symposium on the subject was published in 1942.¹⁰⁻¹⁴ Most recently, Volini and his co-workers¹⁵ discussed various explanations for these sudden deaths and in their paper announced for the first time some of the results of the author's experiments with these drugs which he had given to them in June, 1944, in a personal communication.

The reported fatalities and toxic reactions should not discourage the rational use of mercurial diuretics. They should, however, serve as a warning of what can be expected in rare instances, particularly when such agents are used promiscuously.

It is a pharmacologic truism that every drug is a poison and, conversely, almost every poison may have a medicinal or therapeutic value.¹⁶ The more we investigate the various factors which determine the difference between "poison" and "therapeutic agent," the greater the benefit to public health.

Thus it is quite logical for the pharmacotherapist, after the discovery of the thromboplastic properties of mercurial diuretics, to turn his attention to other pharmacologic agents which might counteract this undesirable effect without interfering with the useful diuretic properties of these compounds. Such studies are now in progress. Complete physiologic, pharmacologic, and other experimental data will appear in the *Archives Internationales de Pharmacodynamie et de Therapie*.

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AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

II. THE DURATION OF THE T-P INTERVAL AND ITS RELATIONSHIP TO THE CYCLE LENGTH (R-R INTERVAL)

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THE period of electrical inactivity of the heart as recorded in the electrocardiogram by the T-P interval never attracted much attention. In going through the literature, one is struck by the paucity of material on this topic. Lombard and Cope,¹ in 1919, measured the cardiac diastole and systole with mechanical devices and noted that there was a shortening of diastole with increase in heart rate. They also mentioned the fact that diastole shortens much more rapidly than systole. Ashman and Hull² mention the fact that the T-P interval shortens with increase in heart rate and with prolongation of the P-R interval.

As long as the P-R, QRS, and S-T measurements fall within certain limits, they are considered to be normal, according to present criteria. These limits, we know, are quite wide, and suggestions are constantly being made to extend them just a little bit further. Yet it is felt that, in some instances, there are disturbances of cardiac conduction, despite the fact that the P-R, QRS, etc., are at or within the upper limits of normal. At constant cycle lengths, prolongation of the P-R, QRS, and S-T intervals produces a compensatory shortening of the T-P interval. The change in the T-P interval, therefore, should be relatively great because it represents the sum of all the prolongations in the various other components of the cycle. It was decided to determine if a constant relationship between the T-P interval and cardiac cycle length (C) existed. If such a relationship existed, perhaps it could be used in recognizing conduction disturbances early. Before this could be pursued any further, it was necessary to determine the following: (1) Is there a constant, predictable relationship between T-P and C in normal individuals? (2) If such a relationship, or correlation, does exist, how predictable is it? (3) What kind of relationship is it and how can it be expressed? (4) How great is the normal scatter? (5) How does physiologic tachycardia, e.g., the tachycardia produced by exercise, affect this relationship?

METHOD

The procedure in this work was outlined in the first paper of this series.³ The same electrocardiograms were used in both studies. The T-P interval was measured from the end of the T wave (where the T wave returns to the isoelectric line and remains there) to the beginning of the following P wave. In Table I is listed the age distribution of the 495 cases in the series.

TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YRS.)	NO.	AGE (YRS.)	NO.	AGE (YRS.)	NO.
18	19	26	22	34	5
19	60	27	15	35	8
20	50	28	10	36	8
21	63	29	14	37	11
22	42	30	17	38	7
23	37	31	11	39	2
24	38	32	10	42	3
25	32	33	10	44	1
Total				495	

RESULTS AND DISCUSSION

A scatter diagram (Fig. 1) was constructed, plotting the T-P interval against the C measurements in all 1,419 readings. On inspection, there appears to be a definite and constant relationship between the two variables. To determine how great this correlation is, the following was done. Two curves were constructed (Figs. 2 and 3): one shows the average T-P measurement for each C value (Fig. 2), thus making C the independent variable; and the other (Fig. 3), shows the average C reading for each T-P value, making T-P the independent variable. Upon superimposing the two curves (Fig. 4), it is seen that the two variables depend on each other very closely. The correlation is greatest for the C values from 0.465 second to 0.751 second (heart rates about 130-80 per minute), where 70.3 per cent of the cases fall; and for the T-P values 0.071 second to 0.291 second, where 77.6 per cent of the measurements fall. The limits, which correspond to the intersection of the means plus and minus the standard deviation of C and T-P, respectively, are shown by the box drawn in Fig. 4. This area includes 66.1 per cent of all the measurements. The degree of correlation expressed by the coefficient of correlation⁴⁻⁶ was calculated (Fig. 5) and found to be plus 0.986; a value of 1.000 representing perfect correlation, and a value of 0.000 representing no correlation. Therefore, this can be considered indicative of a very high positive correlation. Gross inspection and testing by Fisher's method of analysis of variance⁴ showed that the T-P to C relationship is linear. The few measurements that deviate from the curve are probably due to random sampling. Having determined that the relationship of the two variables is linear, the equation for the straight line curve was calculated. Fig. 6 shows the determination of the slope,⁴⁻⁶ and in Fig. 7, A, the close agreement between the actual data and the calculated straight line curve is illustrated. Thus the relationship of T-P to C can be expressed:

$$T-P = 0.737 C - 0.267.$$

The standard error for the prediction of T-P in this equation was found to be 0.026. The preceding can also be expressed:

$$K = \frac{T-P + 0.267}{C},$$

where K is a constant whose value is 0.737 with a standard deviation of 0.048.

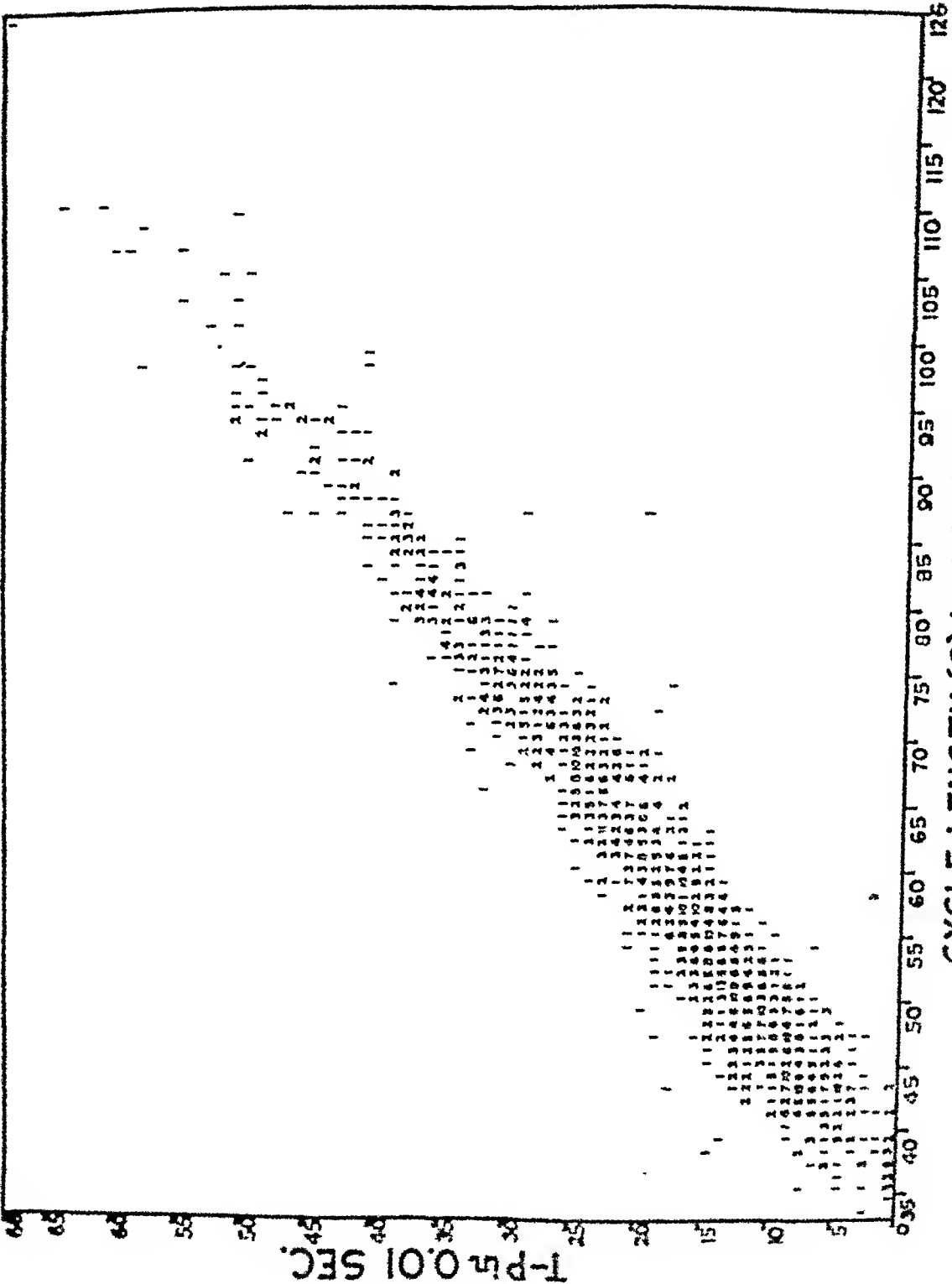


FIG. 1.—Scatter diagram of total readings before and after exercise.

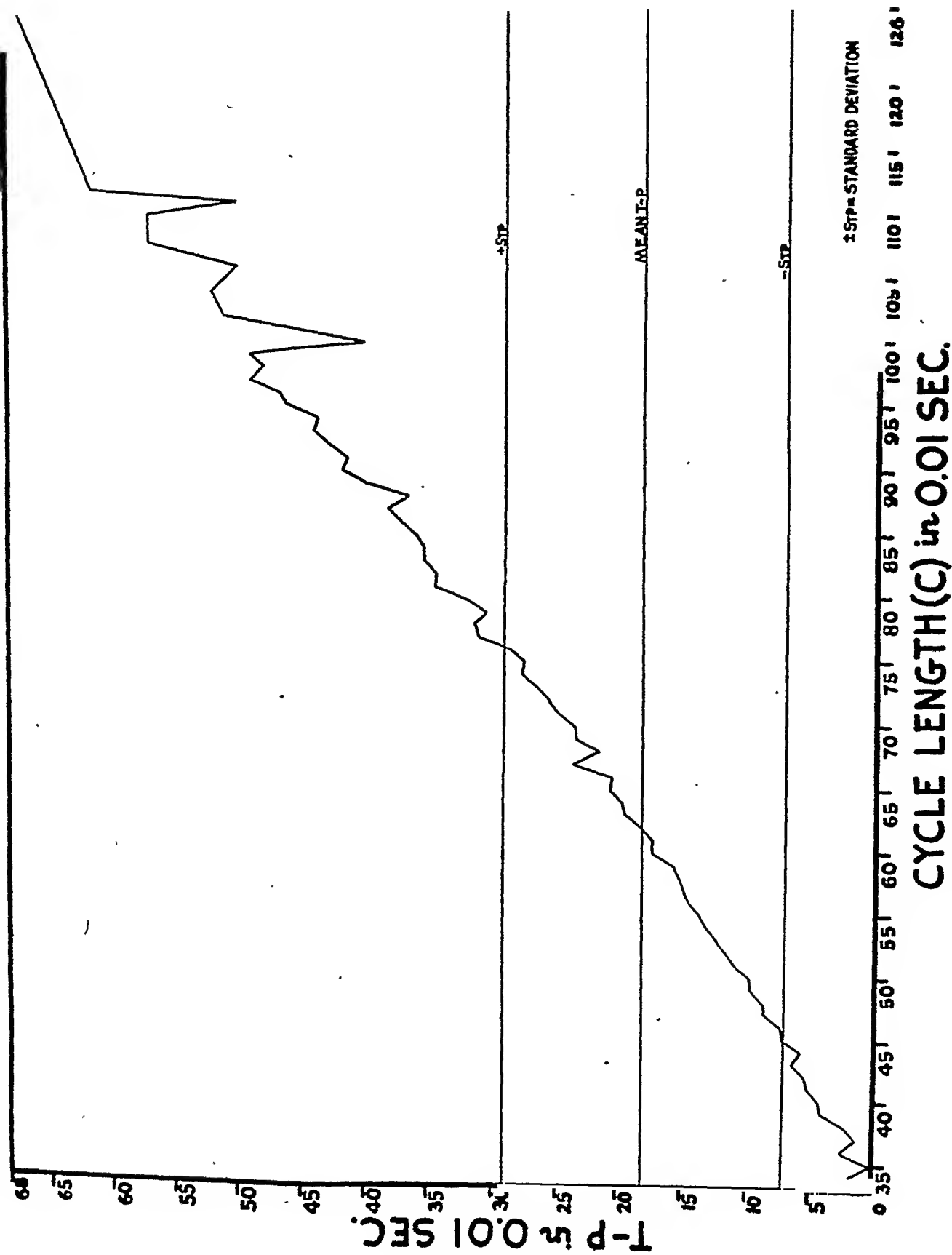


Fig. 2.—Curve showing effect of change in C upon T-P in total readings before and after exercise.

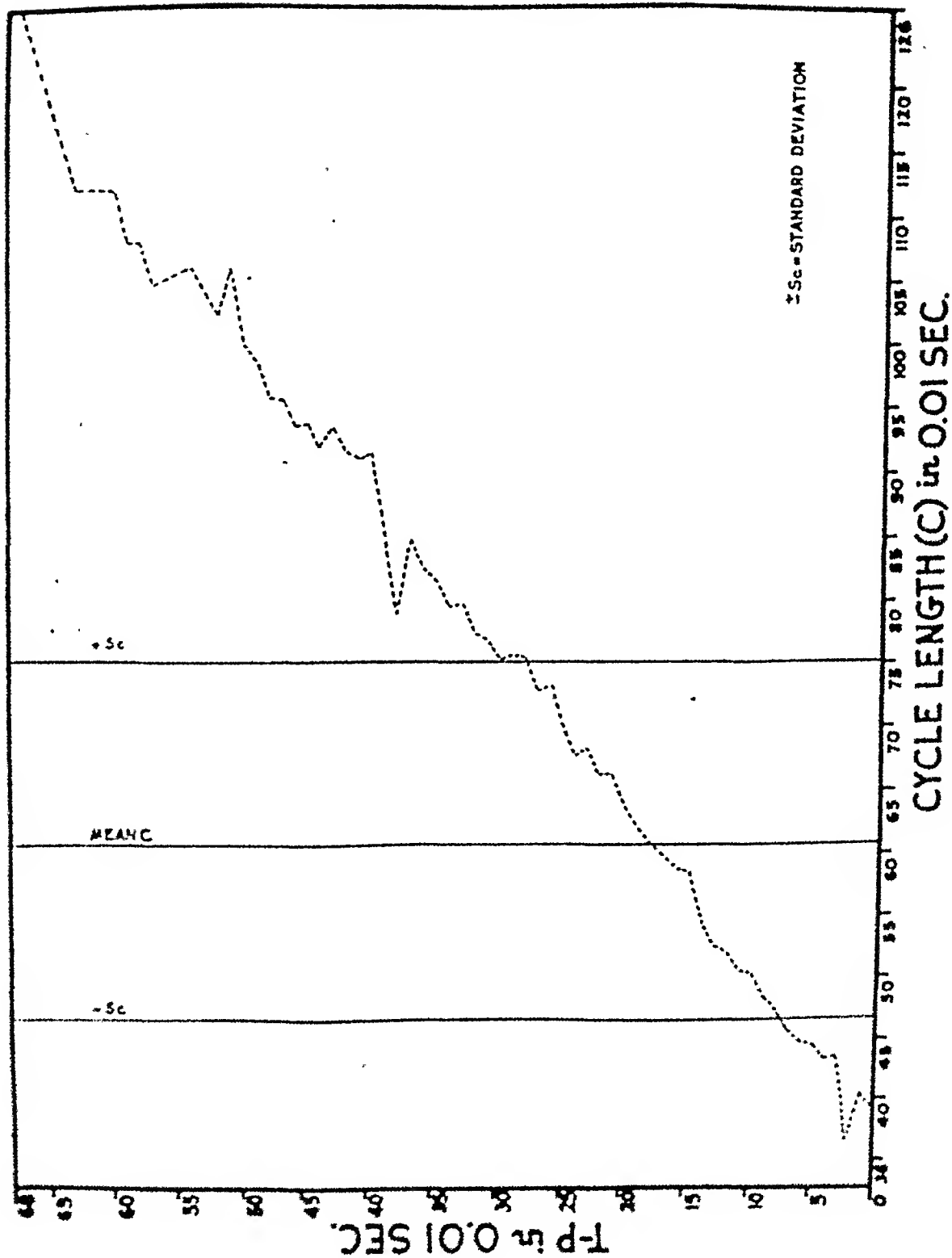


FIG. 2.—Graph showing effect of change in T-P upon cycle length before and after exercise.

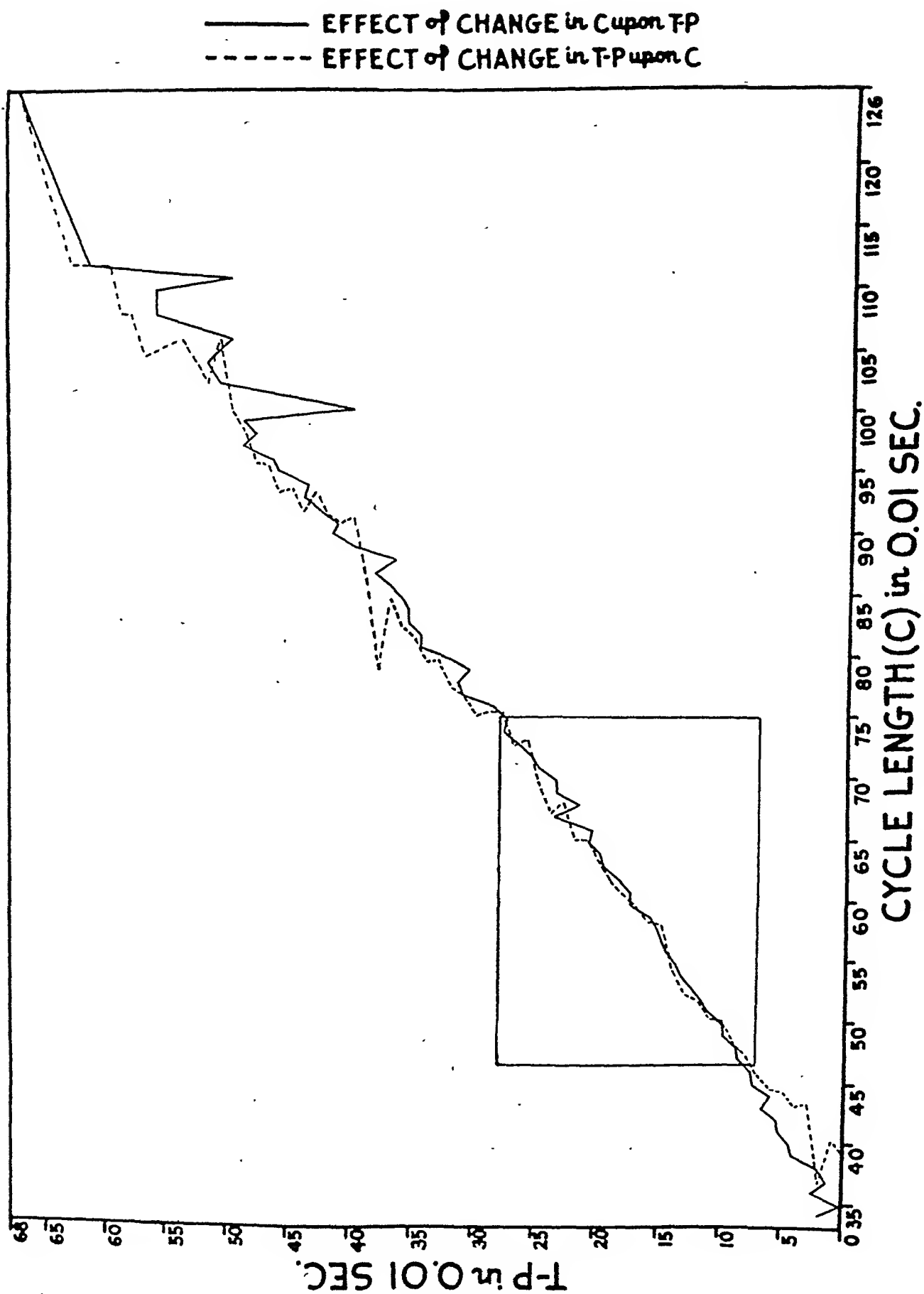


Fig. 4.—Composite curves—total readings before and after exercise.

$$r = \frac{\sum XY - \frac{(\sum X)(\sum Y)}{N}}{\sqrt{\sum X^2 - \frac{(\sum X)^2}{N}} \sqrt{\sum Y^2 - \frac{(\sum Y)^2}{N}}}$$

r = Coefficient

X = C in 0.01 Sec.

Y = TP in 0.01 Sec.

N = # Readings

Σ = Sum of

1. Total Readings Before & After
Exercise

$$r = \frac{21.552}{21.848} = +0.986$$

FIG. 5.—Determination of coefficients of correlation for variables T-P and C.

TABLE II. DISTRIBUTION OF K VALUES IN 1,419 MEASUREMENTS

K	NO.	K	NO.	K	NO.	K	NO.	K	NO.
0.519	1	0.681	9	0.724	25	0.768	16	0.815	1
0.557	1	0.682	1	0.725	2	0.769	5	0.816	3
0.583	1	0.683	2	0.726	24	0.770	6	0.818	5
0.595	1	0.684	6	0.727	16	0.771	7	0.820	1
0.599	1	0.685	12	0.728	12	0.772	16	0.823	4
0.607	2	0.686	10	0.729	10	0.773	10	0.825	1
0.608	2	0.687	2	0.730	21	0.774	14	0.826	1
0.613	1	0.688	2	0.731	5	0.775	4	0.827	4
0.620	1	0.689	6	0.732	10	0.776	6	0.828	4
0.621	1	0.690	9	0.733	13	0.777	11	0.830	2
0.627	1	0.691	11	0.734	21	0.778	13	0.831	4
0.632	1	0.692	10	0.735	14	0.779	4	0.834	2
0.634	3	0.693	11	0.736	11	0.780	13	0.836	2
0.636	1	0.694	8	0.737	30	0.781	13	0.838	4
0.637	2	0.695	10	0.738	12	0.783	7	0.841	1
0.638	3	0.696	7	0.739	6	0.784	6	0.842	3
0.640	2	0.697	1	0.740	9	0.785	6	0.844	2
0.642	3	0.698	14	0.741	16	0.786	11	0.846	1
0.643	2	0.699	2	0.742	2	0.787	3	0.847	1
0.646	4	0.700	9	0.743	11	0.788	3	0.849	2
0.649	2	0.701	4	0.744	7	0.789	13	0.850	1
0.651	1	0.702	9	0.745	37	0.790	5	0.851	2
0.652	3	0.703	17	0.746	10	0.791	6	0.857	2
0.654	1	0.704	16	0.747	4	0.793	3	0.860	1
0.655	1	0.705	16	0.749	27	0.794	7	0.861	1
0.657	4	0.706	11	0.750	10	0.795	3	0.862	1
0.658	2	0.707	9	0.752	13	0.796	1	0.863	1
0.659	1	0.708	7	0.753	6	0.798	5	0.864	2
0.661	5	0.709	8	0.754	24	0.799	4	0.866	1
0.662	4	0.710	6	0.755	5	0.801	3	0.870	1
0.663	1	0.711	12	0.756	16	0.802	6	0.878	2
0.667	9	0.712	20	0.757	6	0.803	1	0.880	1
0.668	16	0.714	16	0.758	5	0.804	1	0.883	1
0.671	4	0.715	2	0.759	26	0.805	1	0.885	1
0.672	2	0.716	10	0.760	6	0.806	4	0.914	1
0.673	8	0.717	16	0.761	16	0.807	9	0.922	1
0.674	12	0.718	4	0.762	11	0.808	3	0.926	1
0.675	8	0.719	5	0.763	14	0.809	2	0.928	1
0.677	7	0.720	17	0.764	15	0.810	1	0.932	2
0.678	3	0.721	12	0.765	18	0.812	3	1.011	1
0.679	1	0.722	17	0.766	20	0.813	2		
0.680	6	0.723	1	0.767	3	0.814	5		

$$K = \frac{T-P - 0.567}{C} \quad S.D. = \text{Standard Deviation} = 0.041$$

0.567 ± S.D. includes 74.6 per cent of all measurements.
 0.567 ± 2 S.D. includes 95.2 per cent of all measurements.
 0.567 ± 3 S.D. includes 99.7 per cent of all measurements.

$$K_3 = \frac{\sum XY - \frac{(\sum X)(\sum Y)}{N}}{\sum X^2 - \frac{(\sum X)^2}{N}}$$

$K_3 = \text{Slope}$

$X = C \text{ in } 0.01 \text{ sec.}$

$Y = TP \text{ in } 0.01 \text{ sec.}$

$N = \# \text{ Readings}$

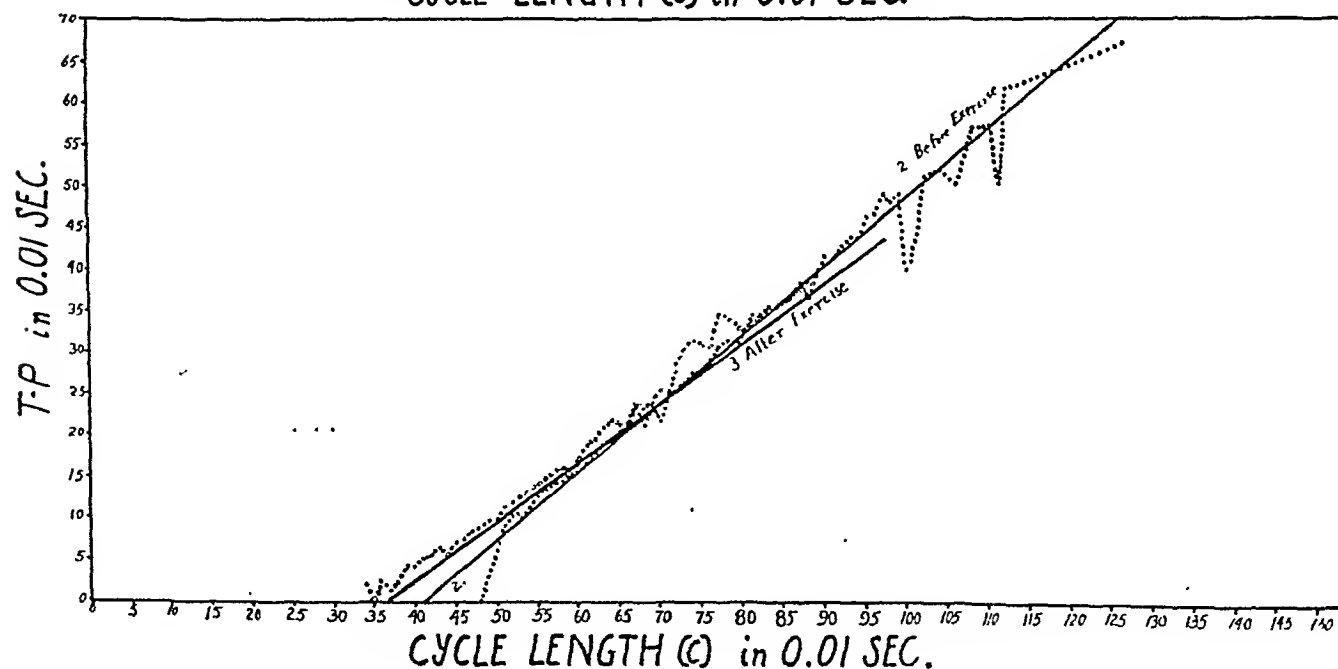
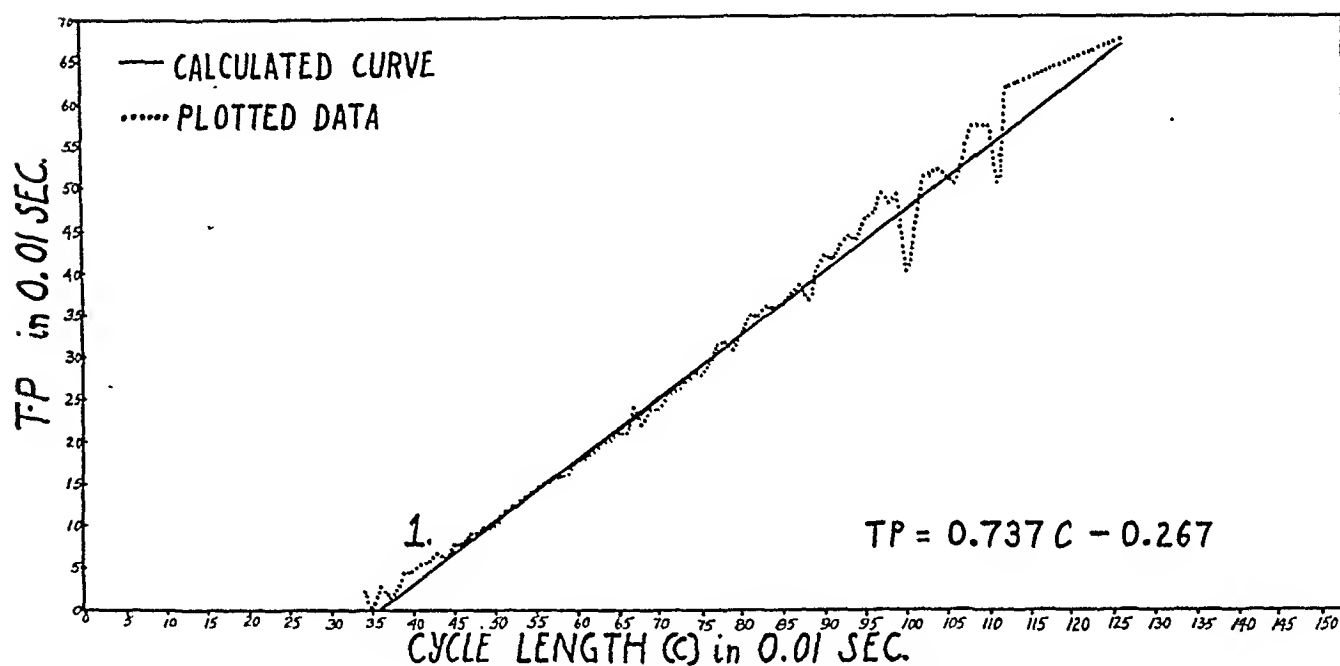
$\Sigma = \text{Sum of}$

1. Total Reading Before & After Exercise

$$K_3 = \frac{21.552}{29.224} = + 0.737$$

Fig. 6.—Determination of slopes of curves for T-P and C relationship.

A.



B.

Fig. 7.—Relationship of calculated to plotted curves. 1, Total readings before and after exercise; 2, before exercise; 3, after exercise.

Table II shows the range and distribution of K values found in all 1,419 measurements. The scatter is not great, for K plus and minus twice the standard deviation includes 95.2 per cent of all the readings. The percentage of readings that falls outside the limits set by K plus and minus three times the standard deviation, beyond which the deviation is considered significant, is small enough (12 measurements) to be considered as due to the error inherent in this study.

The data collected before and after exercise were analyzed in the same fashion as the total number of measurements. It was found that exercise did not cause any significant change in the T-P to C relationship. Fig. 7, B, illustrates the actual data and the calculated curves, both before and after exercise.

As mentioned in the previous paper,³ the curve and equation arrived at as a result of this investigation, represents the composite of all the curves derived from the measurements of the electrocardiograms of many individuals. Therefore, in its application to the individual case, variations should be expected. It was found that these remain within the range of values that comprise the normal scatter. When the measurements in the individual subject made at different cycle lengths are plotted, the resulting curve approximates the composite curve in type, and the deviation remains within the normal limits.

The effect of various factors, e.g., carditis, cardiac hypertrophy, drugs, and coronary sclerosis, were not included in this study. Therefore, it cannot be predicted at this time whether the T-P to C relationship and the equation derived for it, will be of any value in studying cardiac disturbances.

CONCLUSIONS

1. In normal young men, there is a constant relationship, with a significant positive correlation, between the T-P interval and the cycle length.
2. This relationship is linear and can be expressed by the equation:

$$T-P = 0.737 C - 0.267$$

or

$$K = \frac{T-P + 0.267}{C},$$

where K is a constant (0.737) with a standard deviation of 0.048.

3. Tachycardia produced by exercise in normal young men does not alter the relationship.

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AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

III. THE DURATION OF THE P-R INTERVAL AND ITS RELATIONSHIP TO THE CYCLE LENGTH (R-R INTERVAL)

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THE P-R interval, or that portion of the electrocardiogram which records the electrical innervation of the auricles and the time of conduction of the electrical impulses across the auriculo-ventricular groove, has been of interest for many reasons. Most of the work on this subject has consisted of attempts to ascertain the "normal" duration, of the P-R interval and its various deviations from the "normal" which disease or other factors produce. However, some investigators have attempted to determine whether or not there was any relationship between the cardiac cycle length and the length of the P-R interval.

After reviewing the literature on this subject, one is left undecided as to whether or not there is any constant relationship between the P-R interval and the cycle length, for the different authors contradict each other. Bazett,¹ in 1920, found that in his series the P-R interval was closely related to the cycle length (R-R). He expressed the relationship by the formula: $P-R = 0.06 - 0.10 \sqrt{C}$, where C is the cycle length in seconds. The readings, however, deviated quite a little from the predicted curve, and Bazett explained this as being due to factors such as fatigue. Pardee² states that the P-R interval shortens with increases in the heart rate. However, he does not propose any formula to express this relationship, nor does he describe, just how close this relationship is.

Since then this subject has been investigated by other workers with varying results. One group ^{4, 5, 9, 10} found that the P-R interval becomes shorter with increase in the heart rate, but no formulas were proposed to express this relationship. Scheer and Albers,^{6, 7} however, found that not only was there a constant relationship between the P-R interval and C, but they also proposed a formula to express this relationship. Their equation is: $P-Q = 1.73\sqrt{C}$. It is notable that all equations thus far proposed indicate that the P-R interval—cycle length relationship is curvilinear. In 1936, Shipley and Hallaran³ and, in 1940, Benedetti⁸ found that, in their series, they could not find a constant relationship between the P-R interval and the cycle length.

It was therefore decided to study this subject in a large series of normal individuals to determine the following, if possible: (1) Is there a constant, predictable relationship between P-R and C in normal individuals? (2) If such a relationship, or correlation, does exist, how predictable is it? (3) What kind of relationship is it and how can it be expressed? (4) How great is the normal

SCATTER DIAGRAM SHOWING DISTRIBUTION OF TOTAL READINGS
BEFORE AND AFTER EXERCISE

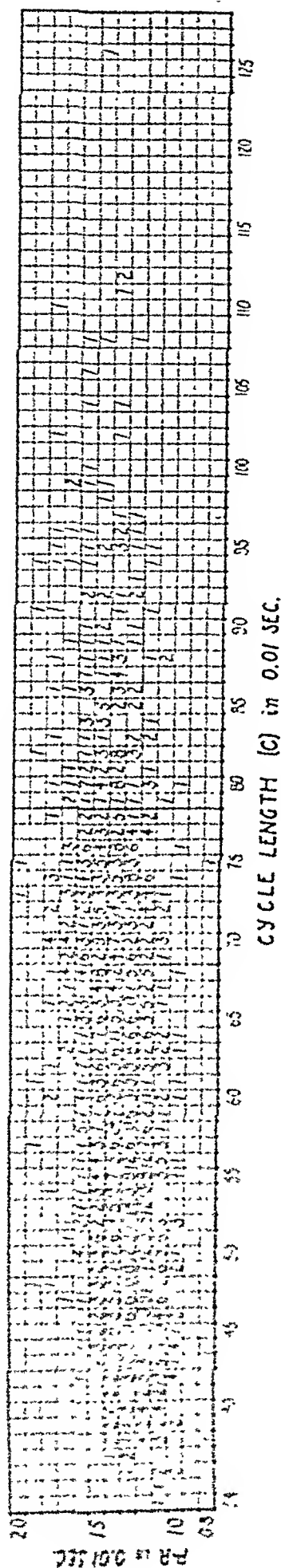


Fig. 1.

scatter? (5) How does physiologic tachycardia, e.g., the tachycardia following exercise, affect this relationship?

METHOD

The procedure in this work was outlined in the first two papers of this series.^{11, 12} The same electrocardiograms were used in all three studies. The P-R interval was measured from the beginning of the P wave to the beginning of the first deflection of the QRS complex. The measurements were made in Lead II, since it was found that they could be made more accurately there than in any of the other leads. Furthermore, the length of the P-R measurements in Lead II were not exceeded in the other leads. In Table I is listed the age distribution of the 495 cases in this series.

RESULTS AND DISCUSSION

A scatter diagram (Fig. 1) was constructed, plotting the P-R interval against the C measurements in all 1,419 readings. On inspection, there does not appear to be a constant relationship between the two variables, although there does appear to be a slight tendency for the P-R intervals to be a little shorter at the shorter cycle lengths. To analyze this data objectively, it was decided to determine the coefficient of correlation.¹³⁻¹⁵ This was found to be plus 0.387; a value of 1.000 representing perfect correlation, and a value of 0.000 representing no correlation. This is indicative of a positive but very low correlation. Statistically, it is not considered significant. It was also found that after exercise the degree of correlation was less than before exercise. That is, the scatter of values became much greater after exercise than before. The coefficients of correlation for before and after exercise were: before exercise, plus 0.440; after exercise, plus 0.195.

TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YRS.)	NO.	AGE (YRS.)	NO.	AGE (YRS.)	NO.
18	19	26	22	34	5
19	60	27	15	35	8
20	50	28	10	36	8
21	63	29	14	37	11
22	42	30	17	38	7
23	37	31	11	39	2
24	38	32	10	42	3
25	32	33	10	44	1
Total				495	

It was then decided to determine whether there was any significant difference between the P-R values before and after exercise. The mean values of the P-R intervals and the standard deviations for before and after exercise are shown in Table II.

It is seen that although there appears to be a tendency for the P-R interval after exercise to be shorter, the difference is more apparent than real. For the P-R values after exercise to be significantly different from those found before exercise, a difference greater than three times the standard deviation should

TABLE II. THE MEAN VALUES OF THE P-R INTERVALS AND THE STANDARD DEVIATIONS BEFORE AND AFTER EXERCISE

	MEAN P-R	STANDARD DEVIATION
Before exercise	0.143 second	0.014
After exercise	0.129 second	0.010
Total readings	0.135 second	0.017

be present. In this series the difference was less than even twice the standard deviation.

In examining Fig. 1 it will be seen that in this series of 1,419 measurements in normal individuals the range of P-R values was from 0.08 to 0.20 second. There were no instances found where the P-R interval fell beyond these values. A check through the records of all cases not used in this study also failed to reveal any instance of a P-R interval prolonged beyond 0.20 second.

Since there is no significantly constant relationship between the P-R interval and the cycle length, this could not be used for the purpose of studying the activity of the conduction system.

CONCLUSIONS

1. In normal young men, there is no significantly constant relationship or correlation between the P-R interval and the cycle length.
2. The duration of the P-R interval before exercise is not significantly different from the values found after exercise.
3. In no case was the P-R interval found to exceed 0.20 second.

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THE EFFECT OF CHANGE OF POSITION OF THE ARM UPON BLOOD PRESSURE

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IF ONE looks at an anatomic sketch of the vascular tree, the blood channels from the heart to the arm are in the shape of a hairpin when this limb is held at the side of the body. When the arm is abducted 90 degrees from the side, the hairpin curve is eliminated and the vessels are more or less at a right angle. When the arm is hyperabducted* 180 degrees, the subclavian, axillary, and brachial arteries are in a fairly straight line. Theoretically speaking, the more direct the pathway, the less is the pressure head of the blood column diminished in overcoming the resistance of a circuitous route. If this assumption is correct, blood pressure should be lowest when the arm is in the first position, intermediate in the second, and highest in the last. This conception might also help to explain the marked difference in pressure between the upper and lower extremities, as the path in the latter is much more direct. Such a pressure gradient has been the subject of much speculation and study in the past.

PROCEDURE

With these considerations in mind, it was thought that, if the patient were stabilized in the supine position and the effect of gravity eliminated by moving the arm into a horizontal plane at the level of the heart, the changes in blood pressure under basal conditions could be due only to alteration in directness of or anatomic interference with the blood flow.

One hundred young adults between the ages of 20 and 35 years were examined in the order of their hospital admission. All of them were well except for trench foot, which was the cause of their hospitalization.

After a blood pressure cuff of standard width (14 cm.) had been snugly fitted above the left elbow, the patients rested on their backs for fifteen minutes. The first fifty patients kept the left arm close to the side; in the second group of fifty patients blood pressures were first taken with the arm hyperabducted. Systolic and diastolic readings were made by the auscultatory method and according to the usual criteria.¹ In order to further minimize experimental errors due to activity of internal organs, emotion, and other nervous influences, the readings were taken approximately three hours after breakfast, by the author, who knew the patients and had taken their blood pressure on other occasions. After a preliminary determination of the approximate levels two readings were taken in succession, and the average was recorded. Such readings were either identical or differed from each other by no more than 2 millimeters. The same Baumanometer, correctly calibrated, was used to take all the readings. For the second reading the arm was moved into the position of hyperabduction by the first fifty patients, and adducted directly to the side by the other fifty patients. After waiting two minutes, readings were taken again with the bell of the stethoscope in the same location as for the initial readings. The blood pressure varied uniformly in the

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*The term *hyperabduction* is not, strictly speaking, a suitable one because the arm is in the midline at its terminal phase. In this article, it will be used to denote the position in which the entire upper extremity is in a line with the long axis of the body, whether the patient is sitting, standing, or lying.

same direction, regardless of whether the arm was first held against the side or in the position of hyperabduction. In twenty patients an intermediate position, with the arm at right angles to the body, was also tried. Readings taken in an intermediate position were illustrative of the general trend but added no special information except in the patients with elevated blood pressure.

RESULTS

Although the readings varied appreciably with change in position of the arm, the direction of change was the reverse of that we had expected: that is, the blood pressure was uniformly higher with the arm at the side than with the arm hyperabducted. The diastolic pressure remained remarkably constant, but the systolic pressure varied from an average of 15 mm. to as much as 20 to 30 millimeters. In one individual when the arm was hyperabducted there was complete absence of pulse.

Twenty-nine patients showed no significant change in systolic or diastolic values. The readings of the remaining 71 patients, expressed in average values, are shown in Table I.

TABLE I. THE INFLUENCE OF THE POSITION OF THE ARM ON THE AVERAGE VALUES OF THE BLOOD PRESSURE IN SEVENTY-ONE PATIENTS WITH NORMAL PRESSURE

POSITION OF ARM	AVERAGE BLOOD PRESSURE (MM. HG)		
	SYSTOLIC	DIASTOLIC	PULSE PRESSURE
Arm at side	122	77	55
Arm hyperabducted	117	76	41

These differences in blood pressure are obviously not due to the effect of gravity or of engorgement of the venous reservoir.

In patients with significant change in blood pressure there was a diminution in intensity of the auscultatory phases, sometimes so marked that the diastolic pressure was difficult to ascertain. There was no change in pulse rate in the different positions.

An analysis of the six patients whose blood pressures were abnormal in one of the three standard test positions is shown in Table II.

In five of these cases, the blood pressure with the arm in a neutral position was normal.

TABLE II. EFFECT OF CHANGING THE POSITION OF THE ARM IN SIX PATIENTS WITH SLIGHT HYPERTENSION

CASE	ARM AT SIDE	BLOOD PRESSURE (MM. HG)	
		ARM AT RIGHT ANGLE TO LONG AXIS OF BODY	ARM HYPERABDUCTED
1	150/82	138/81	126/80
2	158/83	148/84	148/82
3	161/85	146/86	136/84
4	152/76	146/76	145/75
5	174/69	140/61	130/61
6	152/81	144/81	136/82

DISCUSSION

Accuracy in determining the blood pressure requires the avoidance of common errors. This is especially true with regard to the position of both

the patient and the extremity. It is advocated both in this country and abroad that the "patient should be comfortably seated with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface."¹ The supine position can be interchanged with the sitting position, provided notation is made of the fact, since there is no significant difference in blood pressure readings made in the sitting and lying positions.

In the accepted criteria for measuring blood pressure, there is no reference to the position of the arm or the distance it should be held from the side of the body, although it is specified that "there should be no constriction of the arm due to clothes or other objects."¹ It is well known, however, that if the arm is brought too close to the chest wall, external pressure by the latter on the cuff may lead to gross inaccuracies in the reading. Unfortunately, many blood pressure readings are still taken in just this manner.

Other investigators have considered the effect of the position of the arm on hydrostatic pressure and venous engorgement.^{2, 3} Our figures prove quite conclusively that marked deviations of the arm from a neutral, relaxed position away from the side of the body produce appreciable differences in the blood pressure, even though the arm is maintained at the level of the heart. With the arm at the side (0°), the pressures tend to be high; with the arm hyperabducted (180°), they tend to be low.

In six of our subjects, when the arm was placed directly at the side of the body, the systolic pressure was definitely elevated. In five instances, when the arm was abducted, such high readings fell into the normal range. Although extremes of both positions are abnormal, the fact that the pressures were normal in the neutral position is of clinical significance and indicates the importance of rigid adherence to the rules laid down for blood pressure determination.

An interesting phenomenon observed in this study was the lowered blood pressure, and the weakened, and, in rare instances, absent pulse, when the arm was hyperabducted. In a recent article,⁴ Wright demonstrated that when the arm was hyperabducted, the cords of the brachial plexus and the vascular structures to the arm were stretched under the coracoid process and compressed between the clavicle and the first rib or between the scalenus anticus muscle and the cervical transverse processes. Obliteration of the arterial pulse and numbness and tingling, the neurovascular symptoms of the *hyperabduction syndrome*, could be reproduced in such a high percentage of patients that they were not considered to be abnormal. We believe that these anatomic changes described by Wright⁴ are the cause of the variation in blood pressure levels which occur when the position of the arm is changed. We did not find obliteration of the pulse as frequently as Wright, probably because we did not use such adjuvant measures as movement of the head, depression of the shoulder, and pronation and supination of the arm. The difference in the position of the patient may also have had some influence. Wright's patients were examined in the sitting position; ours were examined in the supine position.

Our findings re-emphasize the importance of using a standard position in taking blood pressures. Even minor changes of position, in many indi-

viduals, may result in false readings, which may even be pathologically high or low. Such false readings are sometimes inevitable, as when an anesthetist is forced to take blood pressure readings with the arm in positions demanded by the operation but not suitable for taking blood pressure estimations. The writer recalls a neurosurgical operation during which the anesthetist was extremely concerned throughout the operation over a blood pressure of 70/40, although the patient was in excellent condition and showed no signs of going into shock. The blood pressure was being taken with the arm in the position of hyperabduction.

SUMMARY

Position of the arm has a definite and uniform effect on blood pressure readings. The systolic pressure is lowest when the arm is hyperabducted, that is, when it is made to lie along the long axis of the body. The systolic pressure becomes higher as the arm is adducted and brought toward the side of the body in the horizontal plane. A neutral position of the arm, 45 to 90 degrees from the side of the body, is probably the optimum position for the estimation of blood pressure. Other positions may cause a marked discrepancy in blood pressure readings.

Acknowledgment is made to Colonel Irving S. Wright for helpful criticism and suggestions.

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ELECTROCARDIOGRAPHIC CHANGES IN SCRUB TYPHUS FEVER

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SCRUB typhus, or tsutsugamushi fever, is an acute infectious disease characterized by an abrupt onset, a remittent fever lasting from two to four weeks and terminating by lysis, a maculopapular erythematous eruption that persists for eight to twelve days, and marked prostration. The etiological agent is the *Rickettsia orientalis*, and transmission is by a mite larva. Primary pathologic changes include a vasculitis and a perivasculitis involving the parenchyma of the various organs with a slight tendency to thrombus formation.

Abnormalities of the cardiovascular system are a frequent complication during the acute attack in many of the cases. There is a protracted duration of the convalescent period which is associated with symptoms of extreme physical weakness. In some patients, symptoms referable to the cardiovascular system persist. Because of this, a study of the electrocardiographic changes present during the convalescent stage of the disease was undertaken. The electrocardiograms upon which this study is based were taken from six to eight weeks after the onset of the illness. The diagnosis was confirmed in all cases by a typical clinical course and positive agglutination reactions against *Bacillus proteus* OX (Kingsbury strain).

The patients observed consisted of 78 adult men, 64 of whom were under 30 years of age; the other 14 were less than 40 years old. All were white, with the exception of one who was a Negro. None of the patients gave histories of previous heart disease or of rheumatic fever. The physical examination in all patients revealed no evidence of organic heart disease. The blood pressure was within normal limits. Electrocardiographic studies were made in all cases without regard for the presence or absence of symptoms. All tracings were taken in the recumbent position. Routinely, the three standard limb leads were used, and in 41 cases (52.5 per cent) an additional single precordial lead (IVF) was made.

The standards of normal which were used were those suggested by Katz.¹ (1) P waves were considered abnormal if their duration exceeded 0.11 second, if notching was easily discernible, and if all the waves in the limb leads were smaller than 0.5 millimeter. (2) Low voltage was considered to be present when the QRS complex measured 5 mm. or less in each of the limb leads or when the sum of the amplitude of the QRS complexes in all three leads was less than 15 millimeters. (3) Q and S waves were considered to be abnormal when these waves measured one-fourth or more of the amplitude of the R wave. (4) Devia-

tions of the electrical axis to the left of over 35 degrees were regarded as abnormal. (5) The RS-T segments were considered to be depressed when there were deviations of more than 0.5 mm. in Leads I and II and 0.75 mm. in Lead III. The RS-T segments were considered to be elevated if the deviation was 1.5 mm. or more in the limb leads. (6) In all limb leads only T waves which were less than 1 mm. in amplitude were regarded as being low. Inverted T waves received consideration only when they occurred in Leads I or II. A definitely inverted T wave in the chest lead was regarded as an abnormality.

Symptoms.—Symptoms referable to the heart were present in 27 cases (34.6 per cent). These consisted of tachycardia, palpitation, dull pain in or over the heart, occasional breathlessness, and easy fatigue. Weakness was the only complaint in 12 patients (15.4 per cent). The remaining 39 patients (50 per cent) had no symptoms. Of the 27 patients with symptoms suggestive of cardiac disease, 20 had abnormal electrocardiographic patterns, while seven had tracings that were within normal limits. There were two patients with normal electrocardiograms and ten patients with abnormal patterns in the group of twelve patients whose only complaint was weakness. Of the 39 patients without symptoms, 13 gave normal tracings while 26 had some electrocardiographic abnormality. Five of the six patients who developed cardiac decompensation during the acute attack showed low amplitude of the QRS complex. Frequently changes in the electrocardiograms of patients without recognized heart disease were quite striking.

TABLE I. INCIDENCE (IN PER CENT) OF ELECTROCARDIOGRAPHIC CHANGES IN SEVENTY-EIGHT CASES OF CONVALESCENT SCRUB TYPHUS

ABNORMAL CHANGES	TOTAL INCIDENCE	ISOLATED FINDING	ASSOCIATED ECG ABNORMALITIES										PRESENCE OF SYMPTOMS REFERABLE TO HEART
			SINUS TACHYCARDIA	PROLONGED P WAVE DURATION	P-R INTERVAL AT UPPER LIMIT OF NORMAL	PRESENCE OF Q WAVES	DECREASED AMPLITUDE OF QRS	PRESENCE OF S WAVES	RS-T SEGMENT DEVIATIONS	T WAVE CHANGES	PREMATURE CONTRACTIONS	LEFT AXIS DEVIATION	
Sinus tachycardia	46.1	4	-	20	18	9	9	20	15.6	13	2.6	4	13
Prolonged duration of the P wave	29.5	2.6	20	-	12	5.2	2.6	18	6.3	9	1.3	3.2	10.4
Presence of Q waves	12.8	-	9	5.2	4	-	-	4	8	4	-	1.3	4
Decreased amplitude of the QRS complex	12.5	-	9	2.6	1.3	-	-	4	2.6	-	1.3	-	6
S waves in two different limb leads	27	-	8	9	2.6	-	8	-	2.6	5.2	1.3	6.5	-
Associated Q and S waves in different limb leads	5	-	4	2.6	-	-	-	-	1.3	2.6	-	-	-
RS-T segment deviations	29.5	2.6	15.6	6.5	4	8	2.6	13	-	6.5	-	1.3	8
T wave changes in Leads I and II	23	5.2	13	9	6.5	4	-	9	6.5	-	-	-	9
Inversion of the T wave in either Leads I or II	4	1.3	1.3	-	-	-	1.3	2.6	-	-	-	-	-

Heart Rate.—The observed heart rates varied from 60 to 150 per minute. Rates of 100 or more per minute were considered to justify a diagnosis of sinus tachycardia (Fig. 1). This condition was present in 36 patients (46.5 per cent). It was present as an isolated finding in only 4 per cent, while it was frequently associated with other changes such as prolonged duration of the P wave, RS-T segment deviations, and changes in the T waves (Table I). Sinus arrhythmia was present in seven patients but was not significant. Two examples of auricular and one of ventricular extrasystoles were recorded.

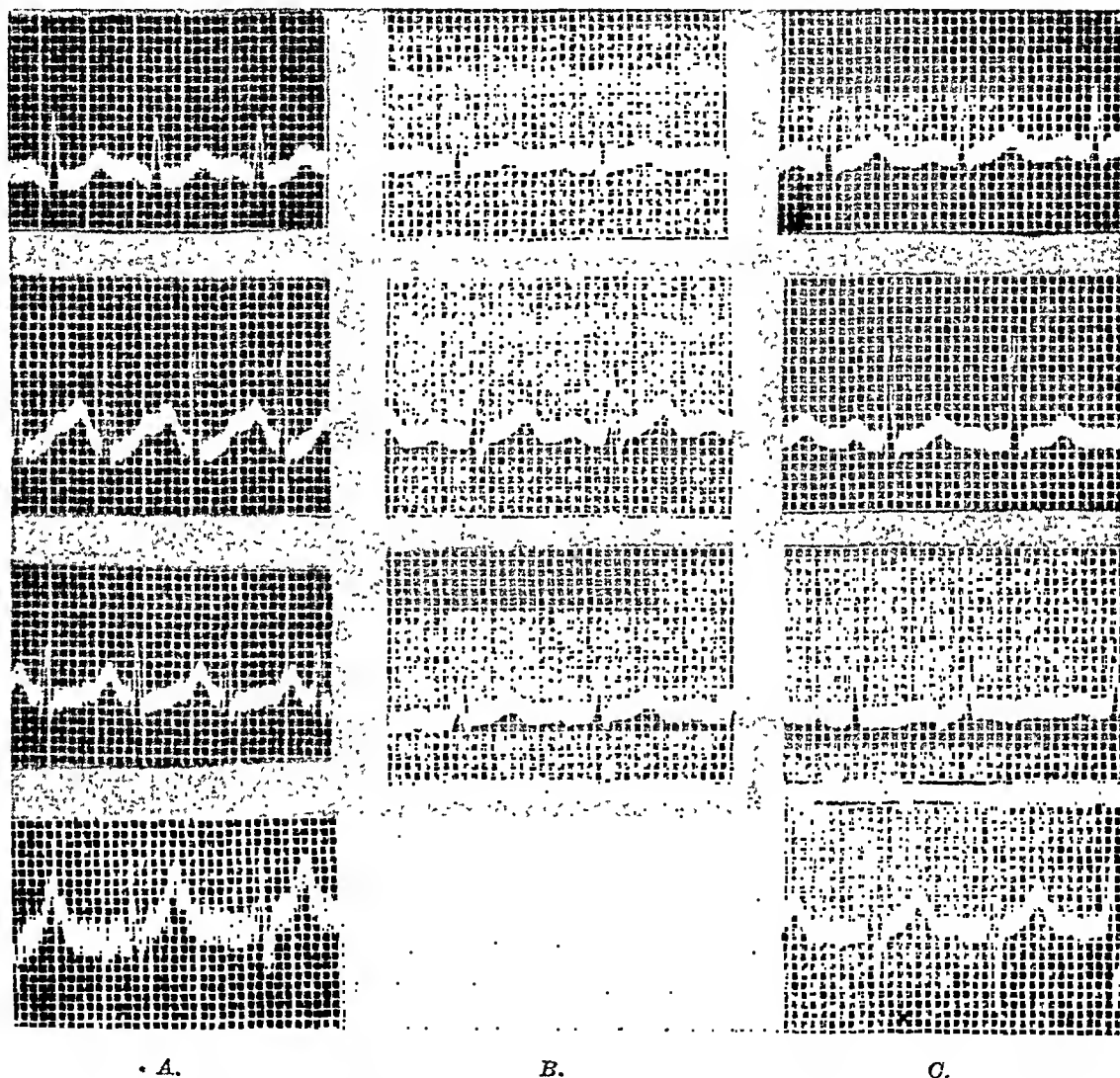


Fig. 1.—Three records showing tachycardia. A, from a patient who complained of extreme weakness and palpitation, shows sinus tachycardia with a rate of 150 per minute. B is from a 28-year-old white man whose only complaint was weakness. The heart rate is 105 per minute with a P-R interval of 0.2 second. C, taken from a 22-year-old white man without symptoms, shows a heart rate of 111 per minute and premature auricular contractions.

P Waves.—Variations of the P waves (Fig. 2) were seen in 29 patients (38 per cent). These waves were abnormally wide in 23 patients (29.5 per cent); while notching appeared in only two. The electrocardiograms of four patients showed low P waves in the limb leads. The P-wave abnormalities were associated with sinus tachycardia; other associated changes were infrequent (Table I). In only one patient were abnormally high P waves seen.

P-R Interval.—Heart block was not present in any of the patients. However, in eight patients the P-R interval measured 0.2 second, and in nine an interval of 0.18 to 0.2 second was found. In all of these 17 patients an accompanying tachycardia was present. P-R intervals bordering upon the upper limits of normal were considered to have doubtful clinical significance, since slight prolongation is frequently seen in the convalescent period of various other infectious diseases.

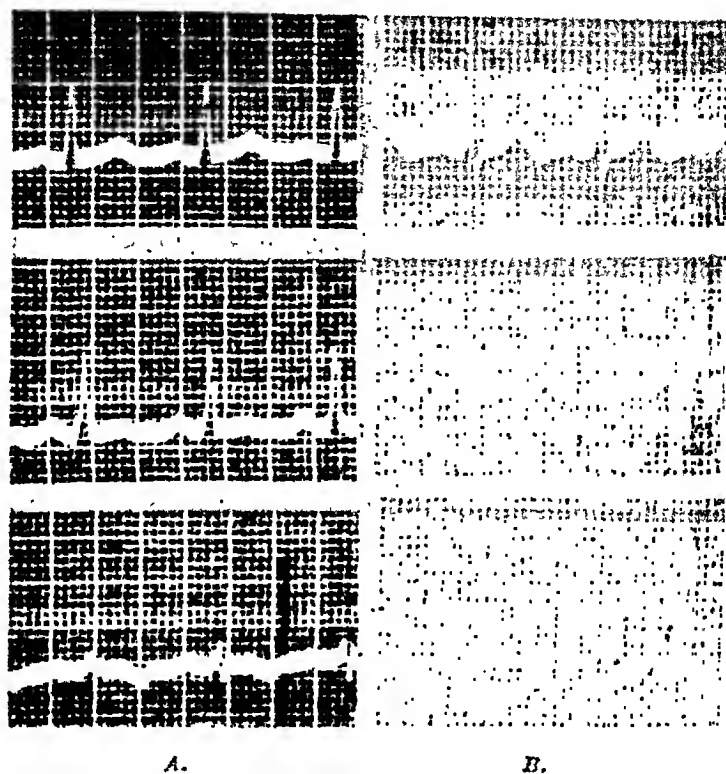


Fig. 2.—Records indicating deviations of the P wave from the standards of normal. A is from a white man, 38 years old, with the complaint of weakness. B is from a 27-year-old white man who complained of palpitation and weakness and shows an increased duration of the P wave.

QRS Complex.—Abnormalities of the ventricular complexes were present in the majority of patients. These included the frequent presence of Q and S waves, low amplitude, and occasionally slurring and notching (Fig. 3). According to the criteria which is being applied, significantly large Q waves were seen in nine patients (12 per cent). In only four of these patients were there associated S waves in another lead. Small Q waves, not exceeding 25 per cent of the upward deflection, were present in 37 other patients. In this study, such small Q waves were considered to be a normal variant.

Deep S waves were present in 41 patients (53.2 per cent). Only those S waves which appeared in two or more of the limb leads were considered to be abnormal. This condition appeared in 21 patients (27 per cent). The QRS complex was of low voltage in ten patients (12.8 per cent). An abnormal duration of the QRS complex over 0.11 second was present in only one patient. Left axis deviation, which could not be attributed to the body build, was present in

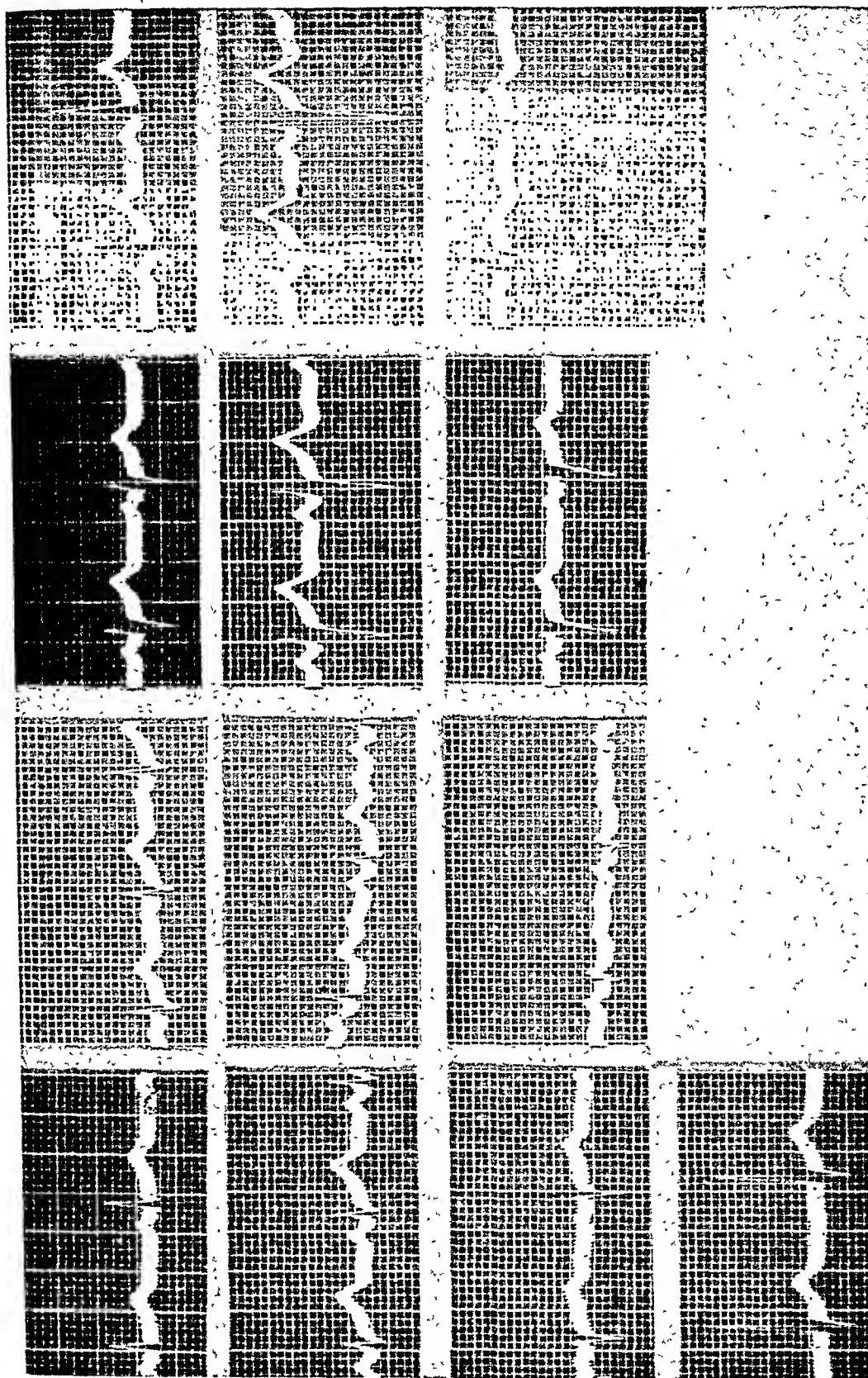


Fig. 3.—Electrocardiograms from four cases showing examples of QRS-complex changes. *A* is from a patient, 35 years old, with no complaints. It shows a heart rate of 90 per minute, with low voltage of the QRS complexes in the limb leads. *B* is from a patient, 30 years of age, who complained of weakness and fatigue. It shows a tachycardia with low voltage of the QRS complexes. *C*, from another patient, 31 years of age, who complained of precordial pain, dyspnea, and weakness, shows deep S waves and left axis deviation. *D* is from a 28-year-old patient who complained of weakness. The heart rate is 90 per minute and left axis deviation is present.

ten patients (12.8 per cent). Deviation of the axis to the right was found only once and in this instance was attributed to the body build of the patient.

RS-T Segment.—Depression of the RS-T segment in the limb leads alone occurred in 12 patients (15.4 per cent). The depression was present in more

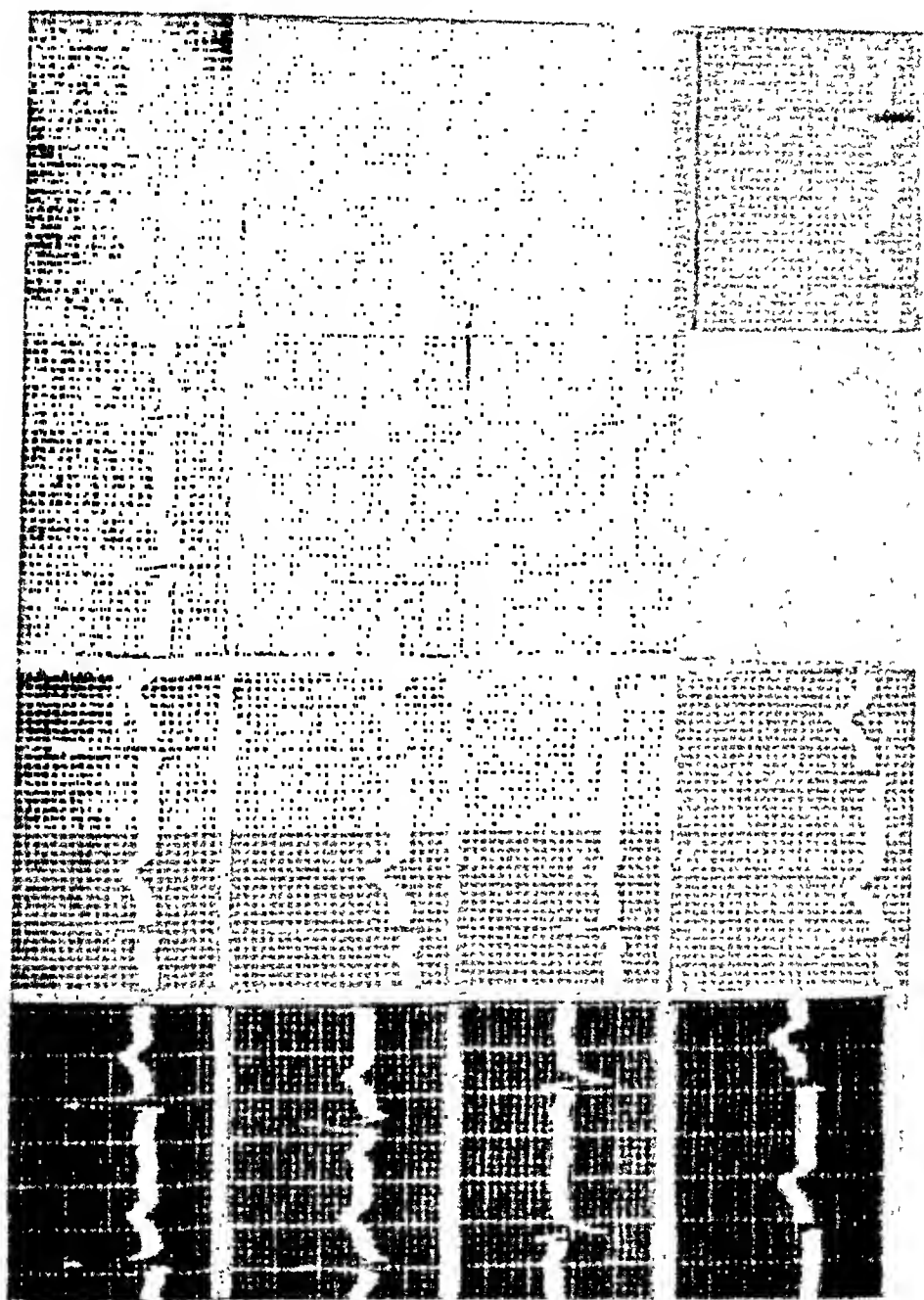


Fig. 6.—Four instances of RS-T segment deviation. A is taken from a 25-year-old white man with complaint of increased pain and weakness, and B is from another 25-year-old white man, both show depression of the RS-T segment. C and D show depression of the RS-T segment. E is taken from a 25-year-old white man with no complaint. F, from a patient aged 27 years, shows a tachycardia of which the patient complained.

than one limb lead in seven of the 12 patients. Depression of the segment was not noted in the precordial leads. Elevation of the segment was observed in 11 patients (14.1 per cent). This change was seen in the limb leads in 10 patients and in the precordial lead in one instance. The elevation was present in Leads II and III in three patients, in Leads I and CFIV in one patient, in Lead I alone in one patient, and in Lead II in five patients. The total number of RS-T

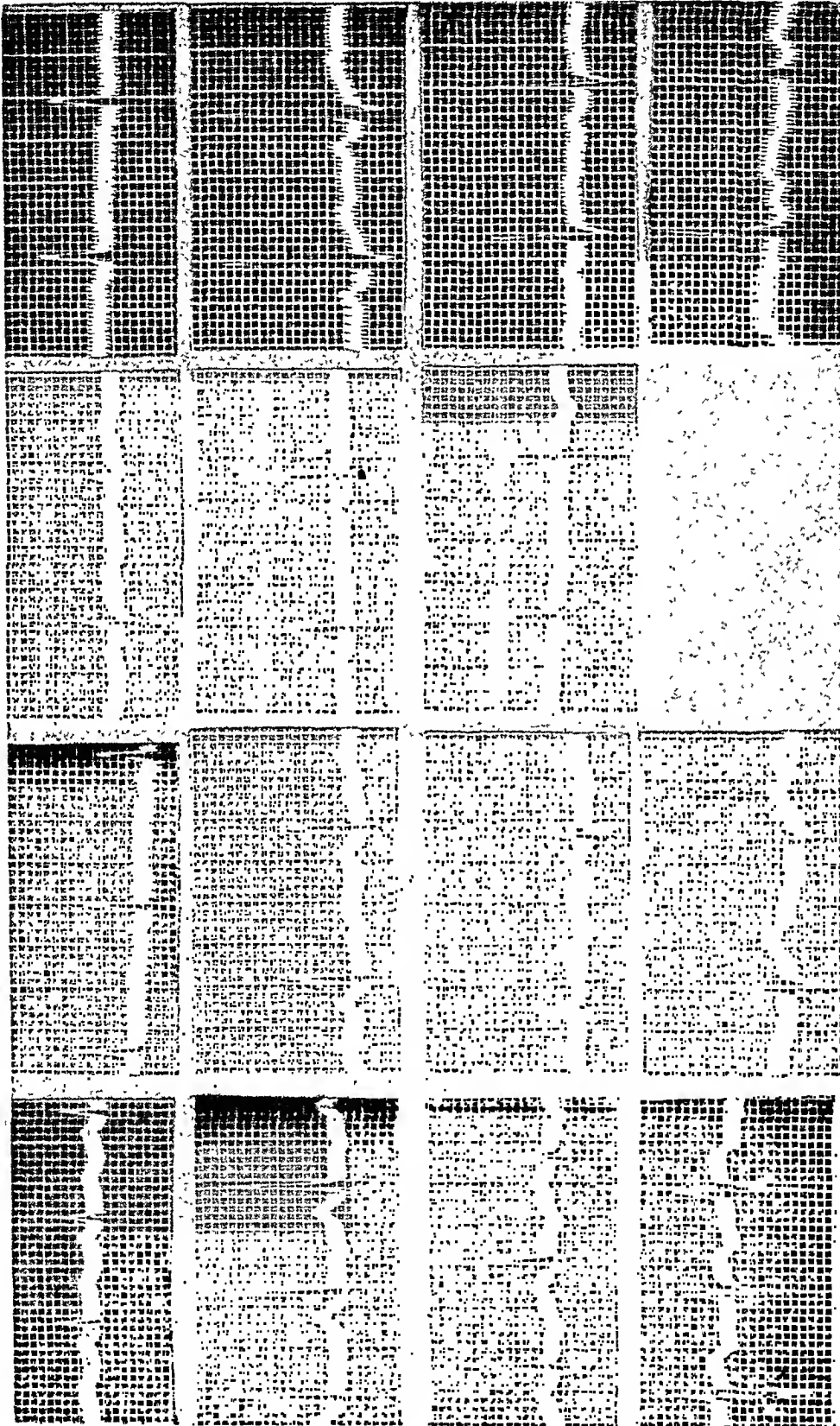


Fig. 5.—Four examples of T-wave deviations. In A, from a 27-year-old white man, there is a low T wave in Lead I, diphasic T wave in Lead II, and an inverted T wave in Lead III. In B, which is from a 25-year-old white man, the heart rate is 120 per minute; an inverted T wave is present in Lead II, and inverted T waves are present in Leads I and II. In C, from another white man, 24 years old, shows a heart rate of 90 per minute; low T waves are present in Leads I and II, and inverted T waves are present in Lead III. In D, from a 22-year-old white man, the rate is 90 per minute; the T waves are low in the limb leads and diphasic in the chest lead.

segment changes totaled 23 (30 per cent). Abnormal deviations were primarily associated with sinus tachycardia and abnormal S waves; in only 6.5 per cent were they associated with abnormal T waves (Table I). No example of both depression and elevation in the same record was recorded (Fig. 4).

T Wave.—In 23 patients (30 per cent) there were changes of the T waves which were confined to Lead III. In 16 of these 23 patients the change was inversion. These changes were considered to be within normal limits. In seven cases low T waves were observed in Lead I or II. Low waves were found in Lead I in three patients, in Leads I and III in two patients, and in all three leads in two patients. Associated with inversion of the T wave in Lead III were a low T wave in Lead I in four patients and low waves in Leads I and II as well as Lead III in four patients. In three cases inversion of the T waves in Leads II and III were associated with a low T wave in Lead I. Changes in the T waves, excluding changes limited to Lead III, were present in 18 patients (23 per cent). Of these only 5.2 per cent were isolated findings (Table I). Peaked T waves in the limb leads were present in two cases. T-wave abnormalities were not noted in the precordial leads (Fig. 5).

Duration of Changes.—The circumstances under which these studies were made allowed the study of only a limited number of these patients for any length of time. From those who could be followed for a number of months, no statistical conclusions could be drawn. In eight cases there was a persistence of the electrocardiographic abnormality as late as five months later, while in two the changes were present one year later. Frequently, the electrocardiogram would become entirely normal within three months of the onset of the infection. In other cases there would be some improvement with only the continuance of a minor abnormality.

SUMMARY

A study of the electrocardiographic findings in 78 patients convalescing from scrub typhus fever is reported. In 34.6 per cent of the patients of this series, symptoms referable to the heart were present. No relationship was found to exist between the subjective symptoms and the electrocardiographic findings. Likewise, no correlation between the severity of the disease and the apparent electrocardiographic abnormalities in the convalescent period could be determined. Patients who developed cardiac failure were more likely to show persistence of multiple abnormalities and to require a more prolonged convalescent period. The tracings of only 13 patients were graded as being within rigid normal limits; in another eight patients there were minor electrocardiographic changes that were placed within normal limits. The remaining 57 patients (73 per cent) showed abnormal electrocardiographic findings as late as six to eight weeks after the onset of the infection. Sinus tachycardia was present in 46.1 per cent and was frequently associated with some other abnormality. Prolonged duration of the P wave appeared in 29.5 per cent. No example of heart block was present. While minor deviations of the QRS complex were quite frequent, associated Q and S waves were present in the same record in only 5.2 per cent of the patients. Large S waves in more than two leads were found in

27 per cent. Low voltage was present in 12.8 per cent of the series. Small Q waves were present in 47.4 per cent of the series. Left axis deviation was seen in 12.8 per cent. In 29.5 per cent of the cases deviations of the RS-T segment occurred, and this was the only finding in 2.6 per cent of the patients studied. The T-wave abnormalities, excluding those in Lead III, totaled 23 per cent. Chest leads, with one exception, were within normal limits.

CONCLUSION

In this series of 78 cases of convalescent scrub typhus fever the electrocardiographic findings in the order of frequency were: (1) sinus tachycardia; (2) RS-T segment deviations, about equally divided between elevation and depression; (3) prolonged duration of the P wave; (4) abnormal S waves in at least two of the limb leads; (5) abnormalities of the T waves of which low amplitude was the most common; (6) left axis deviation; (7) diminished amplitude of the QRS complex; and (8) the presence of Q and S waves in different limb leads. Small Q and S waves were frequently noticed. Under a rigid application of the criteria defining the normal, apparent abnormal electrocardiographic findings were present in 73 per cent of the patients studied. In view of the somewhat wider limits of normal which are now accepted, some of these tracings would possibly be classified as within normal limits. However, the presence of borderline changes and particularly the presence of more than one change in a single tracing may well indicate the continued presence of myocardial damage.

No relationship between the severity of the disease, the subjective symptoms, and the presence and persistence of electrocardiographic abnormalities could be determined.

Acknowledgment is made to Lieutenant Colonel Carl A. Dahlgren and Major Herman Shapiro for their cooperation and helpful suggestions.

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Clinical Reports

PERSISTENT RIGHT AORTIC ARCH WITH ATRESIA OF THE ENTIRE MAIN PULMONARY ARTERY

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VERY early in the development of the human embryo the definitive aortic arch and its branches and the pulmonary artery have their origin in a series of arches that develop between the ventral and dorsal aortae.¹ These are six in number and arise in consecutive order cephalocaudally. By means of atrophy and absorption, certain portions of the arches disappear completely whereas others remain to form the adult vessels as we know them. While the pattern of atrophy and absorption is ordinarily remarkably constant, occasionally it is not, and this results in the formation of a series of anomalies of the larger vessels which also pursue definite patterns.

The most common abnormalities are found in the aortic arch and its branches and consist of coarctation of the aorta, patent ductus arteriosus, posterior right subclavian artery, right-sided aortic arch, and double aortic arch.² Anomalous developments of the main pulmonary artery also occur, but these are considerably less common.

Perhaps the most frequently encountered anomaly of the pulmonary artery is stenosis of the origin of the main artery so constantly found as one of the features of the tetralogy of Fallot. Complete stenosis or atresia at the exit of the main pulmonary artery from the right ventricle has been reported quite frequently.³⁻⁵ Complete or partial absence of the main pulmonary artery has been recorded less often. In 1928, Wheeler and Abbott⁶ reported a case of the latter in a man 29 years of age. In 1931, Kugel⁷ described two cases in infants, and, in reviewing the literature, stated that Abbott collected 31 cases of "truncus solitarius aorticus." Subsequently, a case in a girl 9 years old was reported by Schopper,⁸ one in a boy 5 years old was reported by Greenspan and Leaman,⁹ and one in an infant 9½ months old was reported by Rossman.¹⁰ In the last 1,200 necropsies performed at the Jefferson Medical College Hospital we have encountered eight cases of a posterior right subclavian artery, three cases of a patent ductus arteriosus, two cases of a double aortic arch, one case of a right-sided aortic arch, and one case of a right-sided aortic arch with an atresia of the

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entire main pulmonary artery. The latter is of particular interest because in a review of the literature we have found only one other case in which this combination was present.⁶

REPORT OF A CASE

A white girl was delivered spontaneously at term and for the first two days of extra-uterine life appeared entirely normal. On the third day she developed repeated attacks of cyanosis and was admitted to the Jefferson Medical College Hospital. When the first bottle feeding was attempted at the hospital she suddenly developed deep cyanosis unaccompanied by signs of respiratory or esophageal obstruction. The feeding was immediately stopped and, aided by inhalations of oxygen, her normal color returned. Subsequently cyanosis recurred at each attempt at feeding or on crying. By the end of the day, however, cyanosis became continuous and disappeared only when the child was placed in an oxygen tent. Feedings could now be administered only with a medicine dropper.

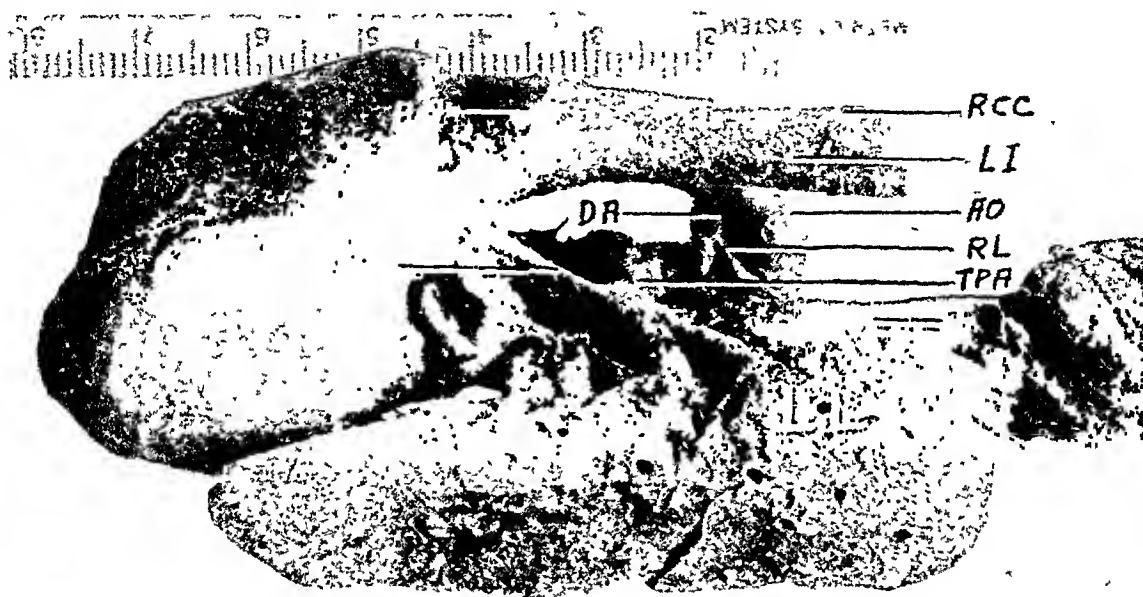


Fig. 1.—Left lateral view showing: AA, ascending aorta; RCC, right common carotid; LI, left innominate; AO, right aortic arch; DA, ductus arteriosus; RL, right recurrent laryngeal nerve; TPA, transverse pulmonary arch; PA, atretic main pulmonary artery; T, trachea; and LL, left lung.

Physical examination revealed the cyanosis of the head and neck already referred to. There was a slight shift of the trachea to the right at the suprasternal notch, a lag in the expansion of the chest on the right, impaired percussion, and diminished breath sounds over the right upper lobe. There were no abnormalities on percussion or auscultation of the heart at the initial or subsequent examinations. A roentgenogram of the chest on the day of admission revealed an atelectasis of the upper lobe of the right lung, a slight displacement of the esophagus and mediastinum to the right, and a normal-appearing heart shadow. A bronchoscopic examination by Dr. Louis H. Clerf disclosed a normal larynx, trachea, and main bronchi, with no apparent obstruction of the bronchus to the right upper lobe. A culture of the bronchial secretions yielded *Streptococcus viridans*, a member of the Friedlander group of organisms, and *Neisseria catarrhalis*. An electrocardiogram disclosed a right axis deviation compatible with a congenital heart lesion. Some clubbing of the finger tips was noted on the sixth day after admission. A second bronchoscopic examination on the ninth day did not reveal any changes. Cyanosis continued and the child died on the fourteenth day of extrauterine life.

At necropsy the entire main pulmonary artery originating at the base of the aorta and ending in a "transverse pulmonary arch" was represented by a solid fibrous cord that

measured 1.5 by 0.1 cm. (Figs. 1 and 2). The left pulmonary artery was widely patent and measured 0.4 cm. in diameter and 1 cm. in length from the entrance of the fibrous cord to the hilum of the left lung. The right pulmonary artery was directly continuous with the left and from the entrance of the atresic main pulmonary artery to the hilum of the right lung measured 1 cm. in length and 0.5 cm. in diameter. At a point 0.4 cm. from the hilum of the right lung it received a patent right ductus arteriosus that measured 1.5 cm. in length and 0.4 cm. in diameter. This entered a persistent right aortic arch just distal to the junction of the arch with the ascending aorta. The ascending aorta measured 2.3 cm. in length and 1.2 cm. in diameter and at the arch gave rise to the following main arteries: left innominate, right common carotid, and right subclavian. The aortic arch was directed posteriorly to the right of the trachea and esophagus and ended in the descending aorta which gradually crossed to the left side behind the esophagus. The bronchial arteries were not hypertrophied. The right

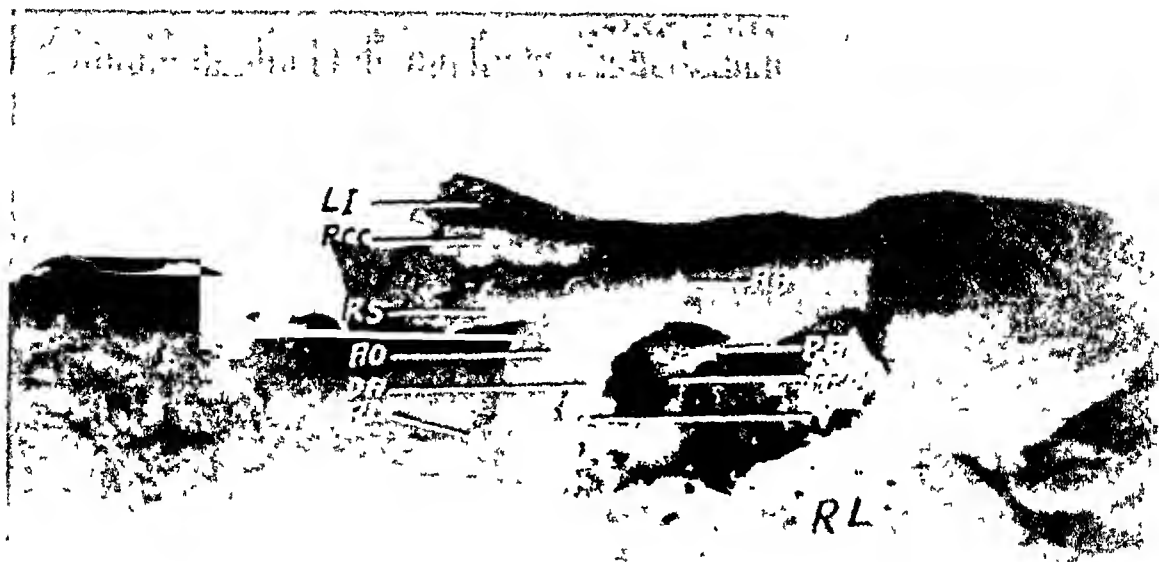


Fig. 2.—Right lateral view showing: AA, ascending aorta; LI, left innominate; RCC, right common carotid; RS, right subclavian; AO, aortic arch; DA, ductus arteriosus; RL, right lung; PA, atresic main pulmonary artery; TPA, transverse aorta; V, vagus nerve; and RI, right lung.

vagus nerve was normal in position and gave off the right recurrent laryngeal nerve as it crossed the ductus arteriosus. It wound around the latter and ascended to the larynx in the tracheo-esophageal groove. The right atrium of the heart was considerably dilated; the foramen ovale was widely patent; the superior four-fifths of the interventricular septum was defective; and the ascending aorta straddled this defect. The lungs showed scattered patchy atelectasis throughout all the lobes and irregular areas of pneumonia. The only other congenital anomalies present were a mobile cecum and a partial failure of rotation of the entire intestines.

COMMENT

The definitive arterial pattern as seen in this case is readily explained on an embryological basis.¹¹ The aortic arch and its branches normally develop from the fourth pair of aortic arches first seen in the 5 to 6 mm. stage embryo. Ordinarily, the fourth arch on the left side persists in its entirety forming the normal aortic arch, while on the right side the dorsal portion between the entrance of the seventh cervical segmental artery (or what later becomes the distal part of the right subclavian artery) and the descending aorta disappears. The

tire ventral portion of the fourth arch thus becomes the proximal portion of the right subclavian artery. The common carotid arteries come from the proximal portions of the third arches. On the left side, this, together with the proximal portion of the aortic sac, is incorporated directly into the aortic arch, whereas on the right side the portion of the aortic sac where the ventral part of the fourth arch joins the right common carotid artery then elongates and forms the innominate artery.

One has, normally, therefore, a left aortic arch giving off in order the right innominate artery, the left common carotid artery and the left subclavian artery (which comes entirely from the seventh left cervical segmental artery). The case reported here is a mirror image of the normal, as just described, so that there is a right-sided aortic arch giving off, in order, a left innominate artery, a right common carotid artery, and a right subclavian artery.

The pulmonary arteries arise from the sixth aortic arches, which first appear in the 6 mm. stage of the developing embryo. As a result of growth and absorption, the proximal portions persist as the main pulmonary artery and the right and left branches, whereas the distal portion on the right side disappears and that on the left forms the ductus arteriosus. In our case the main pulmonary artery became atresic and was represented by a fibrous cord, but there was a direct communication between the right and left pulmonary arteries, forming a normally functioning transverse pulmonary arch. The portion of the left sixth arch that usually forms the ductus arteriosus had disappeared while that on the right side was represented by a widely patent vessel. It was by means of this right ductus arteriosus that the pulmonic circulation was maintained receiving both aerated and nonaerated blood from the ascending aorta.

The literature on a right-sided aortic arch has been adequately covered several times, and a summary need not be repeated here.^{12, 13} This anomaly of itself usually produces no symptoms until later life.^{14, 15} when, as a result of sclerotic changes, the aorta may dilate and press upon the esophagus, trachea, or right recurrent laryngeal nerve. In the case reported by Herringham¹⁶ a dilated aorta produced right-sided laryngeal paralysis and death from tracheal compression. Jex-Blake¹⁷ reported a case of a right aortic arch in a puppy where a short ductus arteriosus coursing first to the left and then behind the esophagus produced esophageal obstruction. Other signs and symptoms that may be elicited are: suprasternal pulsation, stridor, hoarseness, cough, pain in the chest, sensation of "pins and needles" in the left arm, difficulty in eliciting the left radial pulse, and a pulsating tumor indenting the wall of the trachea and esophagus as visualized by tracheoscopy and esophagoscopy.^{13, 14, 18} Since most of the cases are asymptomatic, an ante-mortem diagnosis of a right-sided aortic arch rests with the roentgenologist.^{19, 20} Of importance is a widening of the upper mediastinal shadow to the right instead of to the left and, fluoroscopically, a pulsating aorta to the right of the trachea. When the left aortic arch persists as a diverticulum there may be an aortic knob on both sides of the upper mediastinum. Examination of a barium-filled esophagus shows a characteristic concave depression on the right side at the level of the pulsating shadow, while in the right anterior oblique view the depression is seen on the posterior wall of

the esophagus, and both the esophagus and trachea are displaced anteriorly. Finally, arterial radiography²¹ allows direct visualization of the aortic arch to the right of the trachea and above the hilum of the right lung. Because our case exhibited cyanosis alone it is unlikely that the right aortic arch contributed to its symptoms. A single film of the chest showed no abnormal arterial shadows. Barium studies of the esophagus and arteriography were not attempted because the child was too ill, but bronchoscopic examinations disclosed no tracheal compression.

Although a right-sided aortic arch produces few if any symptoms, stenosis or atresia of the main pulmonary artery is rarely asymptomatic. Cyanosis and dyspnea are usually present from birth,^{5, 7, 10} and if the patients live beyond infancy there may develop clubbing of the fingers, a precordial thrill, systolic and diastolic murmurs over the precordium, polycythemia, and venous distention of the neck. Death results from cardiac failure or intercurrent infection.^{5, 7, 9}

The prognosis is not good and depends on the extent of the collateral circulation which, however, cannot be ascertained clinically. The arteries that may establish a collateral circulation²² consist of the ductus arteriosus, the bronchials, and the mediastinal, esophageal, precordial, coronary, and aberrant arteries from the aorta or subclavian artery. From a study of the cases that came to necropsy it would appear that the best prognosis occurs in those with hypertrophy of the bronchial arteries. In the nine cases reviewed in this report, those showing a closed ductus arteriosus and hypertrophied bronchials^{5, 9, 22} lived to the ages of 5, 16, 20, and 33 years; those showing a partially patent ductus arteriosus and hypertrophied bronchials^{6, 8} lived to the ages of 9 and 29 years, while those with a patent ductus and small bronchials^{7, 10} died at 6 months, 9½ months, and 14 months of age. In our case the bronchials were not hypertrophied; the ductus arteriosus was patent, and the child died at the age of 14 days.

Treatment in stenosis or atresia of the main pulmonary artery has hitherto been entirely symptomatic and at best rather disappointing. The work of Blalock and Taussig,²² however, has changed the entire outlook. In three children showing severe cyanosis resulting from stenosis or atresia of the main pulmonary artery they increased the flow of blood to the lungs by anastomosing the subclavian or innominate artery to a pulmonary artery. Clinically there was immediate improvement in that there occurred a decrease in cyanosis, decrease in dyspnea, and an increase in tolerance to exercise. If this improvement can be maintained there is new hope for an otherwise almost universally fatal condition. This alone justifies the reporting of as many cases as possible in order to enable a more accurate clinical diagnosis.

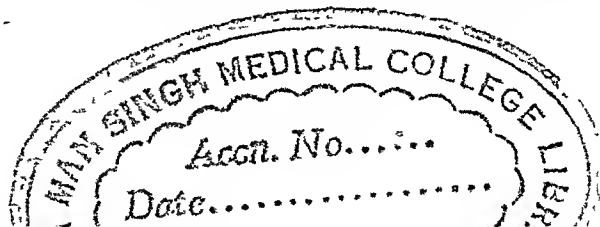
SUMMARY

Of the many anomalies that may arise from the primitive aortic arches present in the developing human embryo, atresia of the main pulmonary artery is one of the least frequently encountered. A combination of this abnormality with a right-sided aortic arch is even less frequent, for the literature contains only one report of such a case. The case presented here is that of an infant who

developed cyanosis two days after birth and died on the fourteenth day of extrauterine life. At necropsy there were found atresia of the entire main pulmonary artery, a right-sided aortic arch, a patent right ductus arteriosus, interauricular and interventricular septal defects, and dextroposition of the aorta.

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PRIMARY, MASSIVE CALCIFICATION WITH OSSIFICATION OF THE MYOCARDIUM

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PPRIMARY, massive calcification of the myocardium with bone formation is very rare. Its occurrence in the myocardium of the left ventricle of an 11-year-old boy was observed at autopsy.

Scholz,¹ in 1924, reviewed the literature on the subject of calcification of the heart and compiled a list of thirty cases. Diamond² reported a 26-week-old premature infant with extensive calcium deposits in degenerated heart muscles. This he attributed to unknown toxic causes. Brown and Evans,³ in 1939, were able to find records of only fourteen instances of primary, massive calcification of the myocardium. Coronary artery disease existed in all but four of these fourteen cases. These authors reported as primary, an instance of massive calcification of the heart muscle which was evidently secondary to coronary artery disease. They stated that massive myocardial calcification usually follows occlusive coronary disease.

CASE REPORT

An 11-year-old white boy was admitted to the hospital because of bradycardia, easy fatigability, and slight cough. The past history disclosed scarlet fever at the age of 6, and rheumatic fever at the age of 7 years. For the past year slight exertion had produced extreme fatigue and epigastric pain. For the past seven months he had been confined to his bed. The physical examination disclosed a poorly nourished child. There were increased breath sounds and moist râles over the lungs. Examination of the heart revealed a loud first sound at the apex, a duplication of the second sound, a questionable third sound and a gallop rhythm. The second pulmonic sound was accentuated. The left border of the heart was at the anterior axillary line, and the apex was felt in the sixth intercostal space. The heart rate was 60 per minute and the arterial blood pressure was 124/85. The liver was considerably enlarged.

During his stay in the hospital the heart rate was 45 per minute on several occasions, and a "swishing" systolic murmur was heard at the left of the sternum in the third or

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Fig. 1.—Heart (left ventricle). Note the marked deposition of calcific material throughout the myocardium.

Fig. 2.—Mitral orifice. Note the narrowing of this orifice brought about by calcific material in the myocardium in the region of the mitral ring.

Figs. 3 and 4.—X-ray pictures of the heart. Note the dense shadows.

Fig. 5.—Microph. (tear) of the myocardium. Iron-haematoxylin-stained preparation, magnification, X130. Note the hyalinization, calcification, and the remnants of muscle fibers.

Fig. 6.—Section of the myocardium. Iron-haematoxylin-stained preparation, magnification, X400. Note the absence of heart muscle fibers in the vicinity of the calcific material, and the moderate infiltration of lymphocytes.



FIG 1.

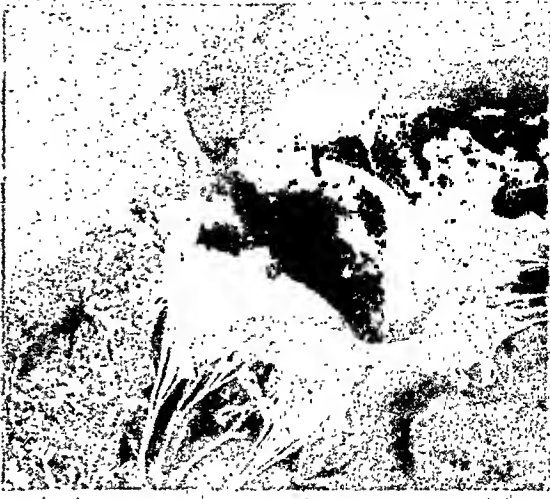


FIG 2.



FIG 3.



FIG 4.



FIG 5.



FIG 6.

fourth intercostal spaces. After the patient was digitalized, a rough presystolic murmur became audible at the apex. The pulse was regular but small in volume. The clinical diagnosis was rheumatic heart disease with mitral stenosis.

The electrocardiographic interpretation was, "Sinus rhythm, with complete A-V block. The idioventricular rhythm arises below the bifurcation of the common A-V bundle" (Fig. 7.) The x-ray examination showed the heart to be markedly enlarged both to the left and right. The lung fields showed a marked degree of pulmonary congestion and there was a small amount of pleural fluid in the right base. The x-ray diagnosis was, "Cardiac enlargement, probably combined mitral pathology."

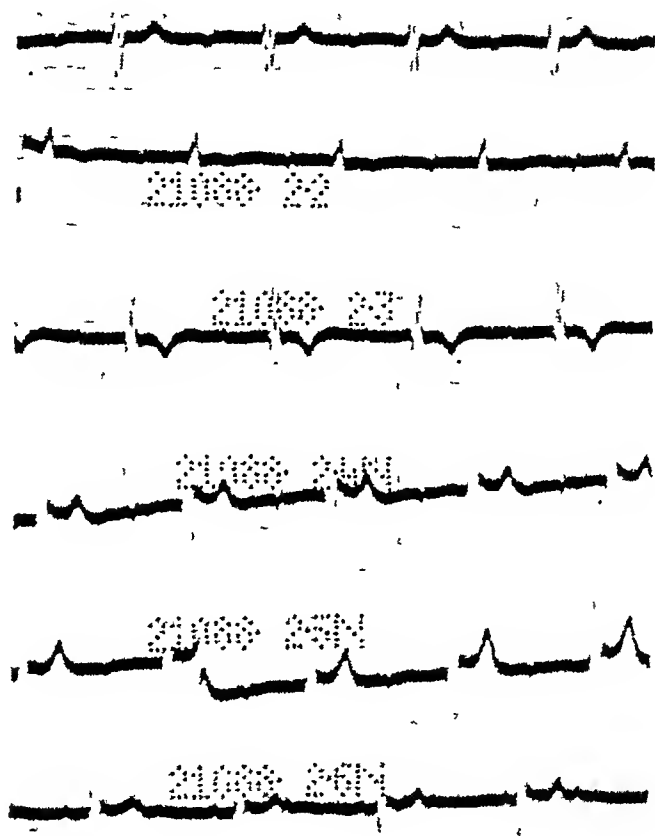


Fig. 7.—Electrocardiogram showing Leads I, II, and III and chest leads CF₁, CF₂, CF₃, CF₄, CF₅, and CF₆. The auricular rate, clearly seen in CF₁, is 94; the ventricular rate is 45. The QRS rhythms are regular; the varying P-R distance indicates complete A-V block. The QRS complex is prolonged, measuring 0.12 second; this indicates origin of the idioventricular pacemaker below the bifurcation of the common bundle.

Repeated blood cultures were sterile. The urinary findings were not abnormal. The red blood count was 5,950,000; the hemoglobin determination, 65 per cent; the leucocyte count, 12,000. There were 57 polymorphonuclear leucocytes, 38 lymphocytes, and 5 neutrophils. The Wassermann and Kahn reactions were negative.

The patient died rather unexpectedly five weeks after admission to the hospital.

At autopsy marked edema was found in both lower extremities. The peritoneal cavity contained 1,000 c.c. of clear straw-colored fluid. Each pleural cavity contained about 500 c.c. of the same sort of fluid. Within the pericardial sac, 150 c.c. of a similar fluid was found. The serous surfaces throughout were smooth and glistening, and there were no adhesions.

The heart was markedly enlarged, weighing 500 grams. It was very firm and the valves which were of stony hard consistency were palpable throughout both right and left ventricles (Figs. 1, 3, and 4). Only very small portions of the heart wall were affected by sclerosis. It was extremely difficult to dissect the heart in the usual easy manner.

calcific masses could not be cut with the knife or scissors, and it had to be opened by means of a hand saw. The valvular apparatus was intact. However, the orifice of the mitral valve was distinctly narrowed by calcific masses which were present in the adjacent myocardium and had severely compressed the mitral orifice which barely permitted the introduction of one finger (Fig. 2). The tricuspid valve measured 8 cm. in circumference, the pulmonic, 6 cm., the mitral, 3 cm., and the aortic, 5 cm., respectively. When the myocardium was examined, it was noted that the left ventricle was almost completely rigid with only isolated portions of relatively normal myocardium. It was difficult to understand how such severely calcified muscle could maintain the function of the heart. The mouths of both coronary arteries were patent. The coronary arteries themselves showed no change. The right ventricle measured 0.5 cm. in thickness; the left measured 1.4 centimeters.

The examination of the remaining organs disclosed a very severe chronic passive hyperemia and terminal bronchopneumonia.

Histologic examination of sections of the myocardium stained with hematoxylin and eosin showed many areas of lymphocytic infiltration in the interstitial tissue, much fibrosis, and large areas consisting of amorphous, bluish material (Figs. 5 and 6). This stained black by the von Kossa method. In many fields, in addition to the bluish amorphous material, unmistakable ossification was noted.

In summary, an 11-year-old child, with severe respiratory difficulties, died as a result of severe calcification of the myocardium.

COMMENT

It is usually stated (Karsner⁴) that pathologic calcification may be divided into dystrophic and metastatic forms. In dystrophic calcification, calcium is deposited in tissues and cells which are the seat of disease. Thus, foci of dense fibrosis, especially if hyalinized, and necrotic masses may become infiltrated with calcium. Dystrophic calcification often attains sufficient size to be seen grossly, as for example, in the wall of the aorta. Metastatic calcification differs from the dystrophic form in that there is no clearly identified tissue injury as a precursor and in that calcium is mobilized from its natural depots. The calcification occurs in the veins, capillaries and alveolar septa of the lungs, in the endocardium of the left side of the heart, in the tunica propria of the acid-secreting parts of the mucosa of the stomach, and in tubules and connective tissue of the kidneys, as well as in other situations. MacCallum⁵ stated that it is questionable whether calcium is ever deposited in the bodies of living active cells, and that one gains the impression that its deposit always occurs in hyaline, inert, interstitial substance, or in dead cells.

Because of the fact that the myocardium was the only region in the body where calcification was present, it seems unlikely that this is an instance of metastatic calcification. It is more likely that the severe myocardial calcification is dystrophic in nature. It seems likely that the calcification was preceded by degenerative and necrotizing lesions in the myocardium.

Among the diseases causing such lesions, diphtheria occupies a prominent place. Ceelen⁶ stated that the toxin of the *Corynebacterium diphtheriae* may produce parenchymatous degeneration and at times even calcification of the myocardium. In one instance of diphtheria he observed partial calcification of the fibers of the right bundle branch and also calcification within the myocardium. Kratzeisen⁷ observed at autopsy the heart of a patient who died as

a result of diphtheria. A deposition of calcium was seen within the diseased muscle fibers.

Also interesting in this respect are the experiments of Albrecht⁸ who seemingly succeeded in producing calcification of heart muscle fibers in rabbits by the injection of *Haemophilus influenzae*. A case of massive calcification of the myocardium of the type reported by Brown and Evans³ is apparently of a different nature since degenerative changes in the heart of this patient were the result of coronary arteriosclerosis with massive calcification.

Although it was impossible to elicit a definite etiological agent for degenerative lesions in the myocardium, which presumably had preceded the calcification of the myocardium, it seems most likely that the patient had either diphtheria or an infection brought about by *Haemophilus influenzae*, since these are the two diseases which more commonly produce degeneration and even necrotizing lesions in the myocardium.

SUMMARY

An instance of massive calcification with bone formation in the myocardium of an 11-year-old boy is reported. No definite etiology for this disease is manifest, but it seems that either diphtheria or infection with *Haemophilus influenzae* had produced degenerative changes and necrotizing lesions of the heart muscle with secondary calcification. The heart was the only organ in the body which showed calcification.

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MULTIPLE DISTURBANCES OF RHYTHM AND CONDUCTION AND UNUSUAL AURICULAR T WAVE IN A CASE OF MYOCARDIAL INFARCTION

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RECENT experimental and clinical reports have stimulated interest in the possibility of making the diagnosis of auricular infarction by means of the electrocardiogram.¹⁻³ The presence of auricular infarction is suggested by disturbances of the auricular mechanism, and by abnormalities in the contour of the auricular complex. The following auricular arrhythmias are encountered: auricular fibrillation, flutter, premature contractions and paroxysmal tachycardia, sinus arrest, wandering pacemaker, and A-V nodal rhythm. Changes involving both the initial and final auricular deflections occur, which are analogous to the evolution of the QRS-T changes which result from infarction of the ventricles. Thus, an auricular Q or S wave may appear, the P wave may be inverted, broadened, increased or diminished in amplitude, notched or slurred, or M- or W-shaped complexes may develop. The auricular S-T segment (P-Q or P-T_A segment) may deviate abnormally, and abnormal auricular T waves may be seen.

The potential differences set up by the final phase of auricular activity are most often so minute as to fail to register in the electrocardiogram. Furthermore, since the total duration of auricular electrical systole exceeds the normal P-R interval, the late deflections are buried in the following QRS complex. In experimental studies the A-V conduction system is blocked mechanically before auricular infarction is produced so that the entire cycle of electrical activity in the auricles is recorded. Since in man the coincidence of auricular infarction with prolonged A-V conduction is rare, little clinical data concerning abnormalities of the final auricular deflection have been accumulated.

It was thought worth while, therefore, to report the following case in which, after an attack of coronary occlusion, multiple disturbances of rhythm and conduction and an unusual auricular T-wave pattern developed.

CASE REPORT

J. G., a 52-year-old Italian man, was admitted to the Cardiac Clinic on May 5, 1943, complaining of shortness of breath and edema of the legs. He was a bartender by occupation and had been a heavy drinker most of his life. He admitted to having had two attacks of gonorrhea but denied syphilitic infection. His wife was a known syphilitic, but repeated examinations in the past had not established the presence of syphilis in the patient. He had considered himself well until July, 1940, when he experienced an attack of substernal pain radiating to the left shoulder. This was followed shortly by severe dyspnea and cough, and

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later by edema of the legs. During the next three years he was admitted to various hospitals on five occasions for the treatment of congestive heart failure. Between bouts of failure he had been able to continue work. Electrocardiograms which were taken during this time on ten occasions showed auricular flutter with varying degrees of incomplete A-V block and right bundle branch block.

The essential physical findings on admission to the clinic were as follows: Dyspnea, orthopnea, and cyanosis were evident. The neck veins were distended. The pulse appeared regular, with a rate of 60 per minute. Blood pressure was 135/80. The heart was enlarged to the left. No thrills or abnormal pulsations were elicited. The rhythm was apparently regular. The first sound was split at the apex, and a faint systolic murmur was audible in this area. The liver edge was palpable 3 fingerbreadths below the right costal margin. The spleen was not palpable. There was no demonstrable ascites. The lower extremities were markedly edematous.

An x-ray film of the chest revealed an old fibrous infiltration of the left upper lobe. The heart was enlarged, chiefly to the left, and there was passive congestion of the lung fields. Electrocardiogram on admission showed auricular flutter with four-to-one A-V block, right bundle branch block, premature ventricular contractions, and ventricular escape beats. The urine showed occasional albumin and showers of hyaline and granular casts. The blood count and blood chemistry were within normal limits. The blood Wassermann reaction was negative.

The diagnosis on admission was (a) arteriosclerotic heart disease; (b) hypertrophy and dilation, coronary sclerosis, myocardial infarction; (c) auricular flutter, right bundle branch block, premature ventricular beats, ventricular escape beats, cardiac insufficiency; and (d) Class IV.

Clinical Course.—The patient was digitalized and placed on a regime of limited fluid intake, salt-free diet, ammonium chloride, and Mercupurin. On July 15, 1943, complete A-V block with auricular flutter and short paroxysms of ventricular tachycardia were noted. This was considered an indication to withdraw digitalis. Five weeks later, auricular fibrillation appeared and digitalis therapy was resumed. On Nov. 4, 1943, while the patient was still on a full maintenance dosage of digitalis, normal sinus rhythm was restored. Coincidentally, there was marked clinical improvement, and aside from dyspnea on exertion, all manifestations of congestive failure disappeared. On Feb. 12, 1944, while walking on the street, he suddenly collapsed; he died shortly after admission to the hospital. Unfortunately, a post-mortem examination was not performed.

ANALYSIS OF ELECTROCARDIOGRAMS

Electrocardiograms were obtained on twelve occasions. Routine findings will be summarized in this section while unusual features will be discussed in detail.

May 20, 1943 (Fig. 1, A): Auricular flutter with four-to-one A-V block was present. The auricular rate was approximately 230 per minute, and the ventricular rate was 58 per minute. The flutter waves were of low voltage. The QRS interval measured 0.14 second and there was right bundle branch block. Occasional premature ventricular beats and ventricular escape beats were seen.

June 3, 1943 (Fig. 1, B): Findings were essentially the same. A precordial lead, which was taken with the exploring electrode placed over the third right intercostal space, demonstrated flutter waves conclusively.

July 15, 1943: Auricular flutter was still present with varying A-V block and intermittent complete A-V block. Lead I was of particular interest (Fig. 2). Auricular flutter was present at a rate of about 222 per minute. The first ventricular complex was indicative of right bundle branch block. The rest

five ventricular beats were of the left bundle branch block type. They occurred in a perfectly regular rhythm, with an R-R interval of 1.52 seconds, and with dissociation from the auricular rhythm, indicating complete A-V block. The bundle branch block then shifted again to the right side, and there was a sequence of three ventricular beats of this type. The change from right to left bundle branch block occurred after a long pause of 1.66 seconds duration, while the shift from left to right bundle branch block occurred after an interval which

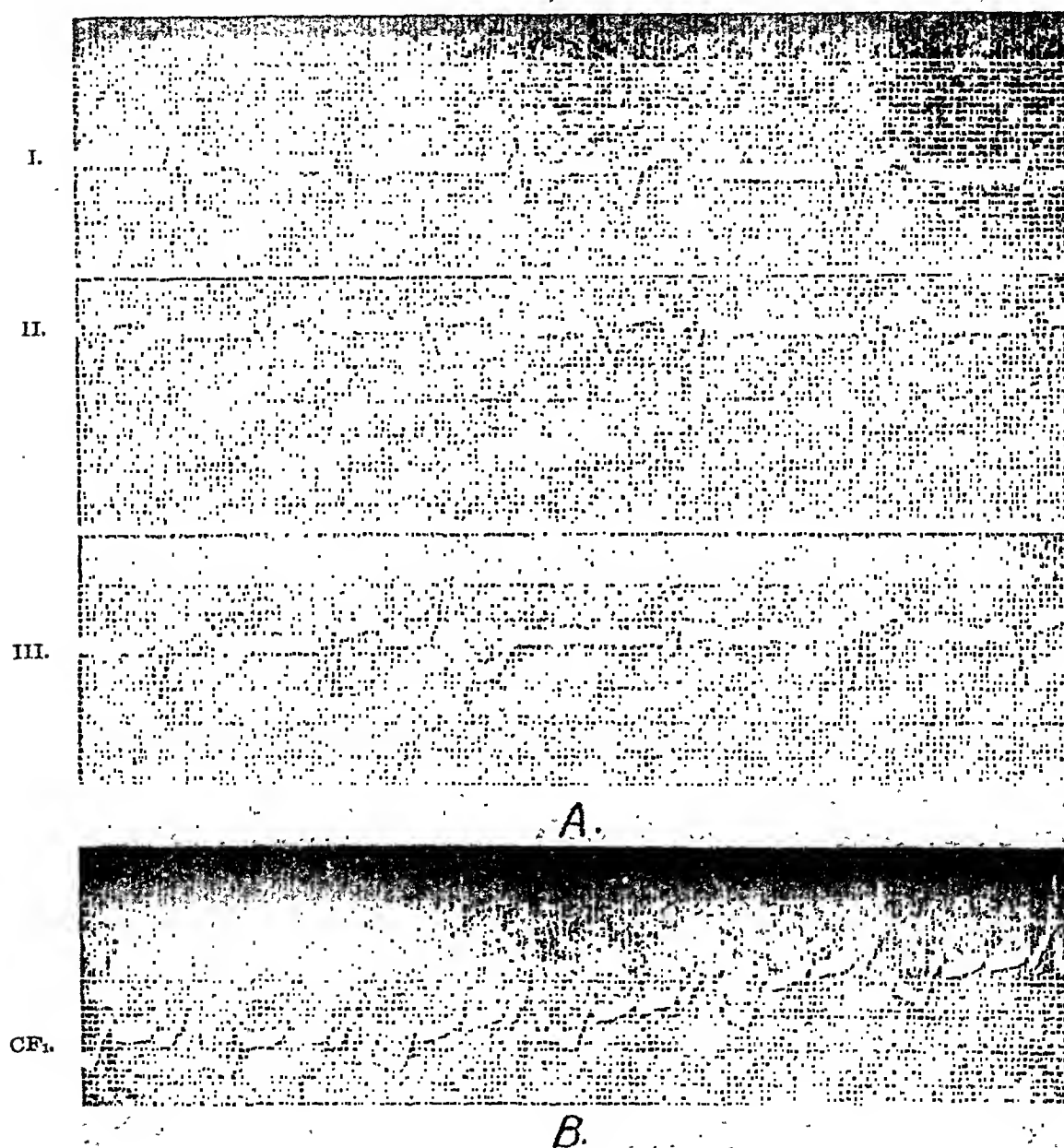


Fig. 1.—A, May 20, 1943. Auricular flutter, four-to-one A-V block, right bundle branch block, premature ventricular contractions, and idioventricular escape beats. B, June 3, 1943. Precordial lead, with exploring electrode over third right intercostal space. Flutter waves are shown more distinctly.

was shorter than that between idioventricular beats, that is, 1.32 seconds. The QRS complexes of the right bundle branch block type were assumed to have been in response to an auricular impulse. This type of complex was seen invariably when either auricular flutter, auricular fibrillation or normal sinus rhythm was present without complete A-V block (Figs. 1, 3, 4, and 6). On

the other hand, complexes of the left bundle branch block type were encountered when complete A-V block was present, either with auricular flutter or normal sinus rhythm (Figs. 2 and 5). This suggests that the idioventricular pacemaker under the latter circumstances was situated in the right bundle branch below the area of block in this bundle. An alternate explanation would be that during

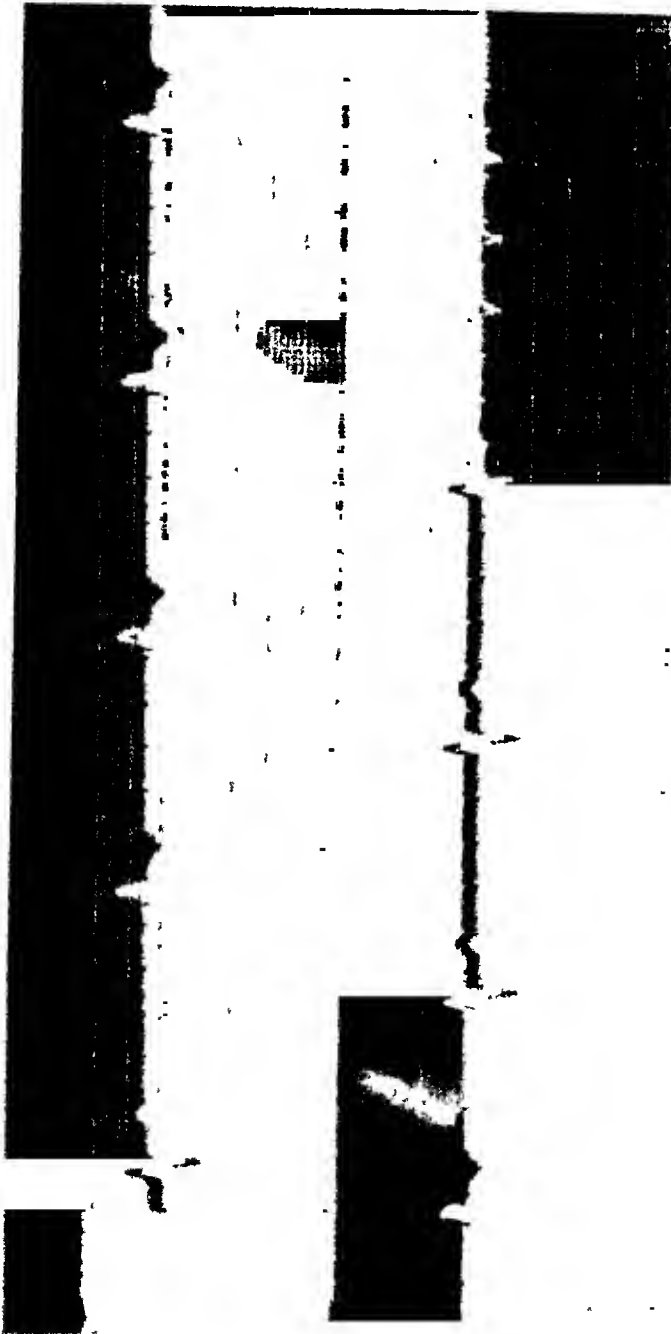


Fig. 2.—July 12, 1942. Lead I, continuous tracing. Auricular flutter. First, seventh, eighth, and ninth ventricular complexes are of right bundle branch block type. Second to sixth ventricular complexes, inclusive, left bundle branch block, and complete A-V block. Last three ventricular complexes constitute a brief paroxysm of tachycardia.

complete A-V block the idioventricular pacemaker might be located above the bifurcation of the bundle. The impulse might then take a slightly different pathway which would allow it to pass through the area of block in the right bundle branch. In support of this hypothesis, when an apparent A-V node

rhythm was present (Fig. 6), the ventricular complexes were of the left bundle branch block type. The last three beats of Fig. 2 were ventricular premature beats, constituting in effect a short paroxysm of ventricular tachycardia. The QRS interval of these beats was shorter than the normal, and, therefore, they probably originated in the region of the interventricular septum.

July, 22, 1943: Auricular flutter, four-to-one block, A-V and right bundle branch block were present.

July 29, 1943: There was no change.

Aug. 26, 1943: Auricular fibrillation and right bundle branch block were present (Fig. 3).

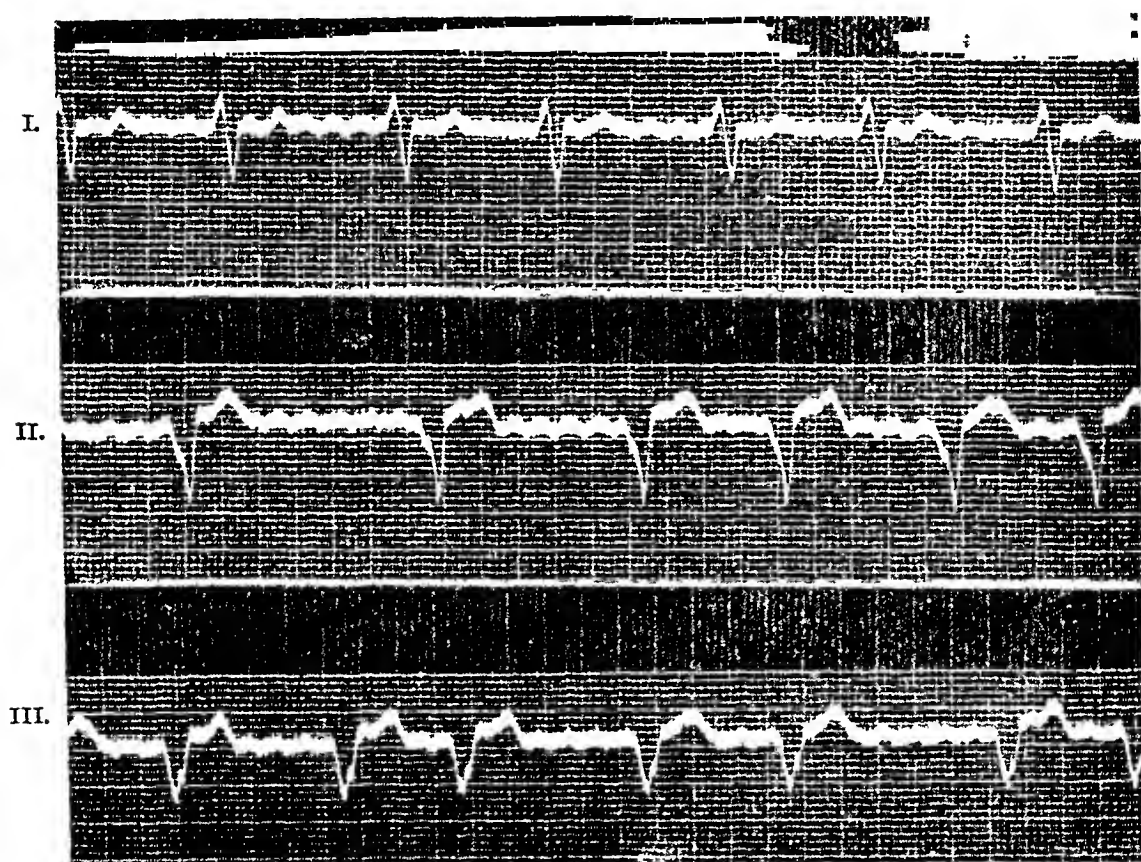


Fig. 3.—Aug. 26, 1943. Auricular fibrillation and right bundle branch block.

Nov. 4, 1943: The strips shown in Fig. 4 were selected from long tracings which were taken on this occasion. The auricular complexes were remarkable for the prominence of the auricular T waves. The P wave was upright in all leads. The auricular T wave was upright to slightly diphasic in Lead I, inverted in Leads II and III, and upright in Lead CF_1 . In Lead III the auricular T wave was more prominent than the P wave. There was no displacement of the auricular S-T segment in the standard leads. It appeared slightly depressed, however, in Lead CF_1 . The dominant rhythm was of normal sinus origin. In the accompanying figure, in Leads Ia, II, and CF_1 there was delayed A-V conduction, with a P-R interval of about 0.44 second. Right bundle branch block was present. Lead I, strip b, showed incomplete A-V block with the Wenckebach phenomenon. The first complex after the dropped beat was a more nearly

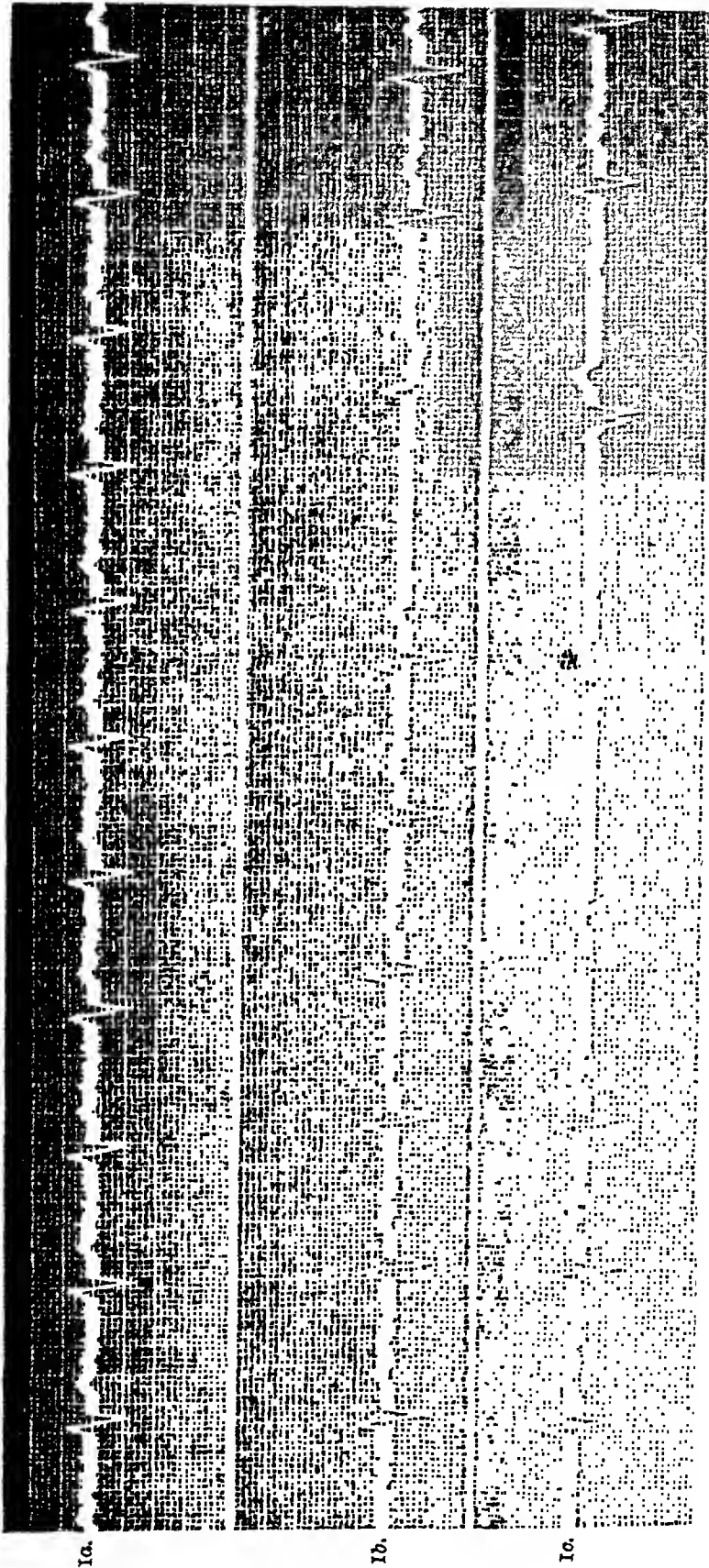


Fig. 4.—(For legend see opposite page.)

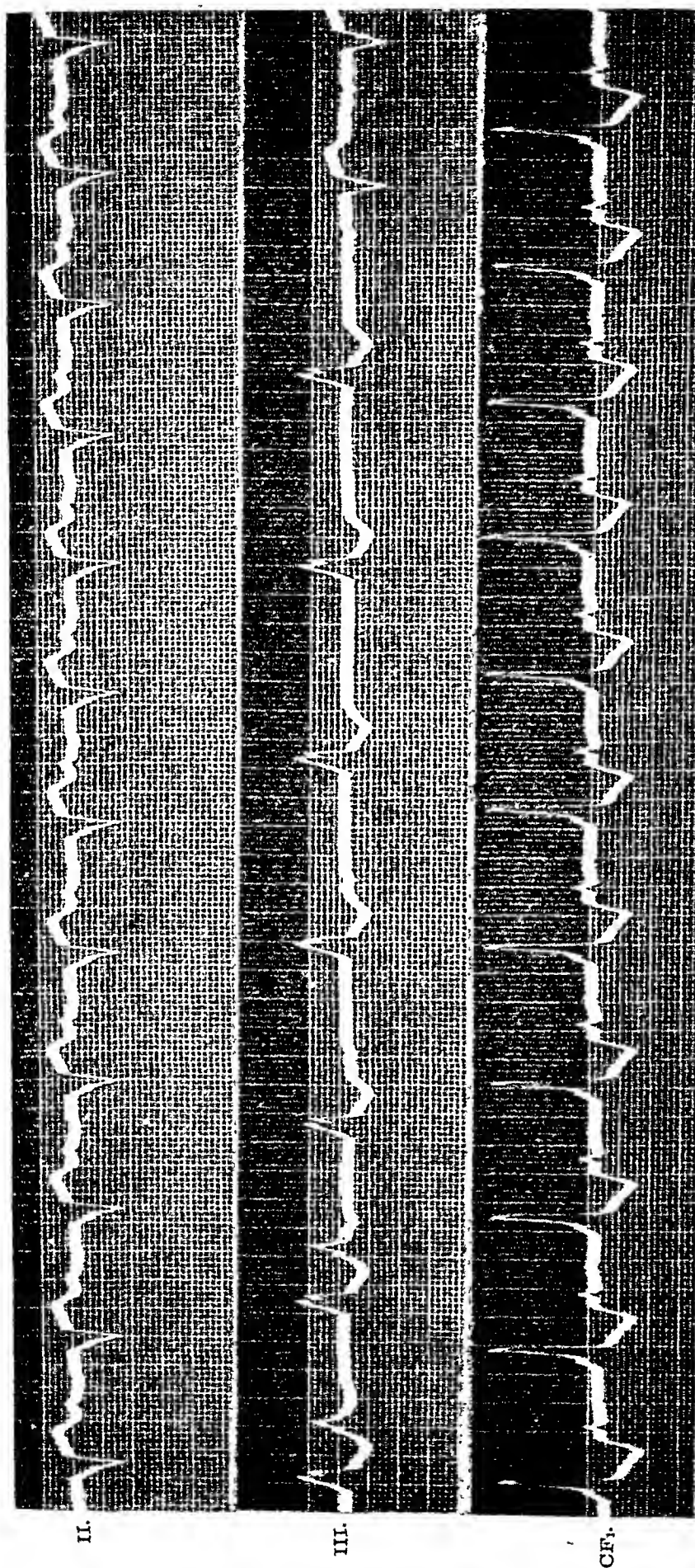


Fig. 4.—Nov. 4, 1943. Leads Ia, II, CF, regular sinus rhythm, prolonged A-V conduction time. Auricular T wave upright to diphasic in Lead Ia, inverted in Leads II and III, and upright in Lead CF. Lead Ib, incomplete A-V block with Wenckebach periods. First QRS complex after dropped beat shows improved intraventricular conduction. Lead Ic, incomplete A-V block, Wenckebach phenomenon, and A-V dissociation with idioventricular escape beats. Lead III, A-V nodal rhythm. First two nodal beats followed by premature ventricular contractions. Last two ventricular complexes are in response to sinus nodal impulses. Auricular T wave is inverted.

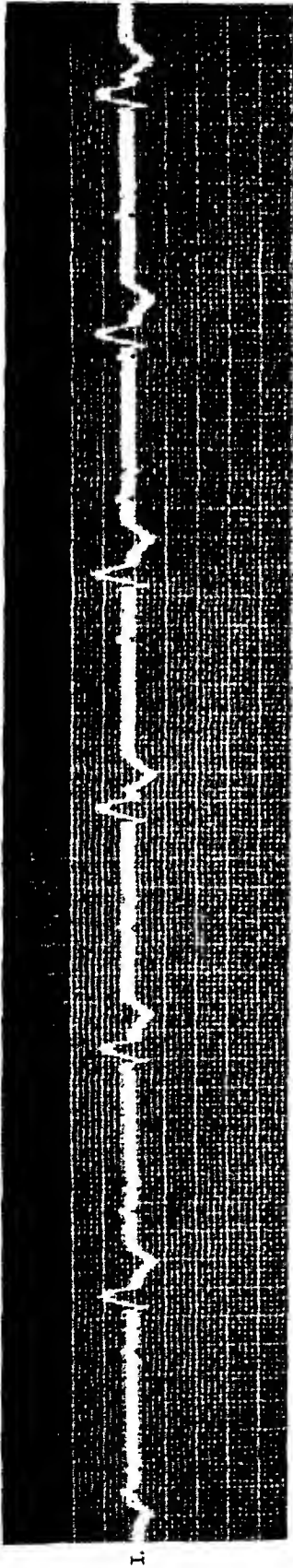


Fig. 5.—Nov. 23, 1943. Lead I. Complete A-V dissociation and left bundle branch block.



Fig. 6.—Nov. 23, 1943. Lead I. Regular sinus rhythm and right bundle branch block. Carotid sinus stimulation followed by A-V nodal rhythm with QRS complexes of left bundle branch type.

normal ventricular complex than the others in the record. It indicated improved intraventricular conduction following the long pause due to the dropped beat.⁴ Lead I, strip c, showed a short interlude of A-V dissociation with idioventricular escape beats. Lead III was of exceptional interest. During the first nine QRS complexes A-V nodal rhythm was present. The first two nodal beats were coupled with ventricular premature contractions which were interpolated. Retrograde P waves were seen clearly following the fourth, fifth, and sixth ventricular complexes after a delayed retrograde conduction time. When the sinus nodal pacemaker resumed command, the QRS complexes changed direction, indicating a change in intraventricular conduction.

Nov. 16, 1943: Regular sinus rhythm, first degree heart block, and right bundle branch block were present.

Nov. 18, 1943: Regular sinus rhythm, first degree A-V block, right bundle branch block, and premature ventricular contractions were present.

Nov. 23, 1943: There were present complete A-V block and left bundle branch block (Fig. 5, Lead I). Normal sinus rhythm and right bundle branch block appeared (Fig. 6, Lead I). After carotid sinus stimulation A-V nodal rhythm occurred, with ventricular responses of the left bundle branch block type.

Jan. 2, 1944: Regular sinus rhythm, first degree A-V block, and right bundle branch block were present. On this occasion multiple precordial leads were obtained. The auricular T wave became more prominent and upright in passing from the right to the left side of the heart.

Jan. 22, 1944: Regular sinus rhythm, first degree A-V block, and right bundle branch block were present. The A-V conduction time was only slightly shortened after intravenous administration of atropine sulfate (0.0012 mg.).

DISCUSSION

Following an attack of coronary occlusion this patient developed multiple disturbances of rhythm and conduction and an unusual auricular T-wave pattern. These features suggested the probability that infarction of the auricular myocardium had taken place. The following auricular mechanisms were recorded: Normal sinus rhythm, auricular flutter, auricular fibrillation, and A-V nodal rhythm. In addition there were premature ventricular contractions, paroxysmal ventricular tachycardia, and idioventricular escape beats. The conduction disturbances included first, second, and third degree A-V block and right and left bundle branch block. Certain aspects of these arrhythmias warrant special comment. The auricular flutter persisted for three years. It was not converted to fibrillation by digitalis, but after discontinuance of digitalis, conversion to fibrillation took place spontaneously. The combination of auricular flutter, and complete A-V heart block is, in itself, a rarity. Gray and Greenfield⁵ in a recent review of the literature found only 31 reported cases and added one of their own. An unusual feature in our case was the presence of left bundle branch block during complete A-V block, and the shift to right bundle branch block when complete A-V block was not present. Fig. 4 was of interest because of the variety of forms of heart block encountered during one examination. Also of interest was the presence of nodal rhythm with

coupled premature ventricular systoles, an unusual form of bigeminy, and the presence of retrograde conduction of the impulse, with marked lengthening of the RP interval. The delayed A-V conduction was organic in origin. It did not disappear when digitalis was withdrawn, and it was not abolished by intravenous atropine sulfate. The carotid sinus was hypersensitive. Pressure on the right carotid sinus regularly produced A-V nodal rhythm, while left carotid pressure produced complete A-V block.

Probably the most interesting feature of this case was the unusually prominent auricular T wave. In Lead I this wave was upright to diphasic, with the upright deflection most prominent, and followed an upright P wave. In Leads II and III the auricular T wave was inverted. In the precordial leads the auricular T wave was upright. It was a fortunate coincidence that the P-R interval was lengthened so that the complete cycle of auricular activity was visible.

CONCLUSIONS

1. Following an attack of coronary occlusion multiple disturbances of rhythm and conduction and an unusual auricular T-wave pattern were seen.
2. These changes suggested that infarction of the auricular myocardium had occurred.

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TRANSIENT BUNDLE BRANCH BLOCK ASSOCIATED WITH TACHYCARDIA

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BUNDLE branch block, once established, tends to remain permanent. The exceptions, in which the block is temporary, have been described as intermittent, paroxysmal, or transient bundle branch block,* and a number of reviews of collected cases have been published. In most of the reported cases, the block occurred or persisted fortuitously and was not rigidly influenced by procedures carried out by the investigator. In a few instances, however, the observers noted that the block was affected by alterations of the cardiac rate. Such cases, in which the bundle branch block occurs only when the cardiac rate is rapid, are extremely rare. The case herein presented is an example of such a phenomenon. Comeau, Hamilton, and White,¹ who reviewed the largest series of cases of transient bundle branch block, stated that in the "routine records of their cases there was no constant correlation between cardiac rate and the degree of intraventricular conduction."¹

Although bundle branch block, either transient or constant, is usually accompanied by other evidence of cardiovascular disease, the case of transient bundle branch block which will be presented is distinguished by the absence of other demonstrable cardiovascular abnormalities.

CASE HISTORY

R. F. W., a 29-year-old man, was hospitalized because of palpitation on exertion. During childhood he had a moderate number of "colds" and sore throats. His general health was otherwise always good and he does not recall having had any serious illnesses. There was no history of rheumatic fever, chorea, scarlet fever, diphtheria, or typhoid fever. Prior to entering the Navy in March, 1944, he was a foreman in a felt hat factory. Since this date he has been occupied principally as mess cook and stevedore in a Naval Construction Battalion. He smoked fifteen cigarettes and drank two cups of coffee daily. He did not use alcohol. His wife, his three children, his father, and one brother are living and well. His mother is said to be nervous and to suffer from sick headaches, fainting spells, and heart trouble. One sister is said to have died of tuberculosis of the spine, and one brother has "leakage of the heart."

Three years before admission to the hospital he noticed that severe physical exertion sometimes caused his heart to palpitate. At first this symptom rarely appeared but later such attacks of palpitation after exercise or violent excitement came more frequently and tended to last longer. Later still these attacks were accompanied by an aching feeling in the precordium. He became dizzy during the attacks, but never fainted.

At the time of his admission into the Navy in March, 1944, his resting pulse rate was recorded as 76 per minute. Two minutes after exercise the rate was recorded as 88 per

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*The term "transient bundle branch block," within the meaning of this article, bears no relationship to the Wolf-Parkinson-White syndrome of short P-R interval with prolonged QRS complex which has been referred to, although incorrectly, as "functional bundle branch block."

minute. His blood pressure was 150/60. It was also recorded at that time that he had a "functional heart murmur with a mild neurocirculatory disturbance."

During the previous year, and particularly during the previous three or four months, these attacks were both prolonged and severe because his work as a stevedore compelled him to do much heavy lifting. When he did not work hard he had few attacks. Invariably, however, after lying down and resting for five or ten minutes, the unpleasant sensations would gradually disappear as his heart slowed.

A review of the symptoms revealed that he had infrequent attacks of bilateral supra-orbital headaches without nausea or vomiting. He also complained of intermittent mild, vague aches of the muscles. At times he experienced mild digestive disturbances such as abdominal distention and an uncomfortable feeling after eating; but these symptoms were never persistent or severe.

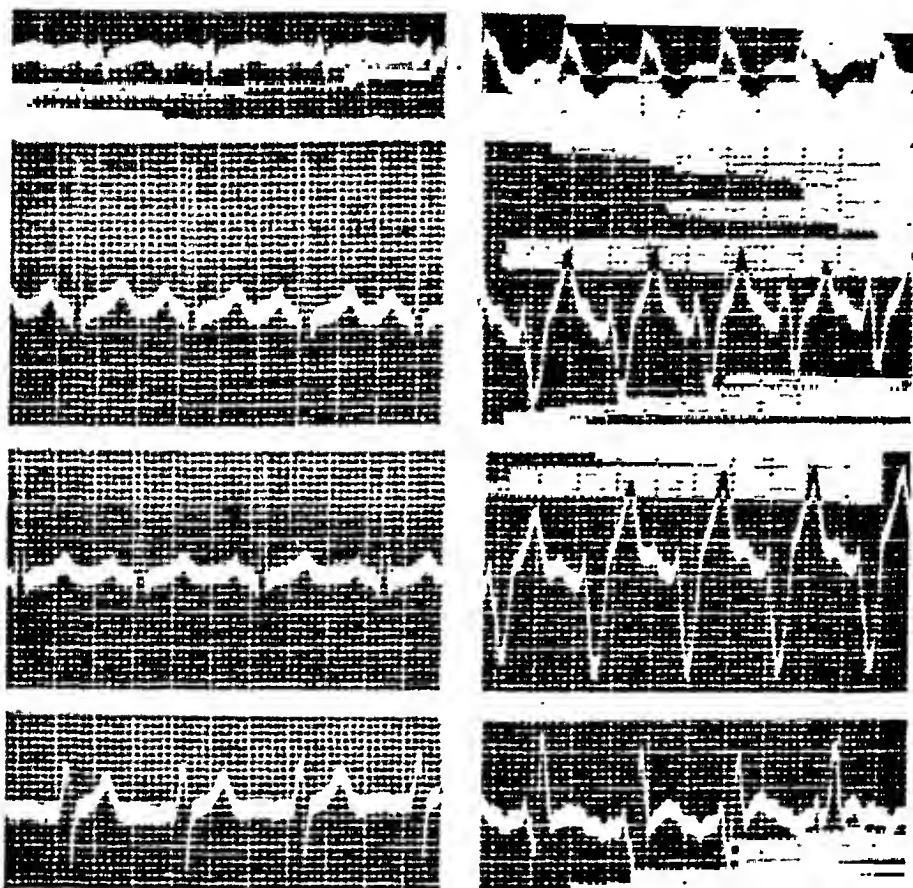


Fig. 1.—R. F. W., aged 29 years. Control (average rate 104 per minute) and bundle branch block following exercise (average rate about 135 per minute).

He was seen in consultation as an outpatient on Jan. 3, 1945. As he performed the Master two-step test,² it was observed that when his heart rate was rapid, a bundle branch block developed (Fig. 1); after he had rested for two minutes, this abnormality disappeared.

He was admitted to this hospital for observation on Jan. 8, 1945. He was of the asthenic type, being 69 inches in height and weighing 135 pounds. The resting blood pressure was 120/70. The resting pulse rate was 84 per minute and the respiratory rate was 22 per minute. The temperature was normal. He appeared to be somewhat anxious and ill at ease. His hands felt cold and he perspired moderately in the axillae. The examination of the eyes, including the eye grounds, revealed nothing significant. Small tonsillar tabs were present. His oral hygiene was poor. Several teeth were broken off at the gingival margins and others were carious.

The heart was not enlarged. No murmurs were heard and no abnormal accentuation or reduplication of cardiac sounds was noted; the heart rate and rhythm were normal. The veins were not engorged and there was no thickening of the peripheral arteries. Fluoroscopic examination of the heart indicated it to be normal in size, position, and contour. An x-ray of the chest showed no abnormalities (Fig. 3).

The blood Kahn was negative. The red blood count was 5,240,000 per cubic millimeter; hemoglobin, 14 Gm.; white blood count, 8,000 per cubic millimeter with a normal differential. The sedimentation rate was 11 mm. in one hour. The serum calcium determination was 10.7 mg. per cent and the blood nonprotein nitrogen was 27 mg. per cent. The concentration and dilution tests showed a range of 1.001 to 1.026 in the specific gravity of the urine. Stool studies were negative for enteric pathogens, ova, and parasites.

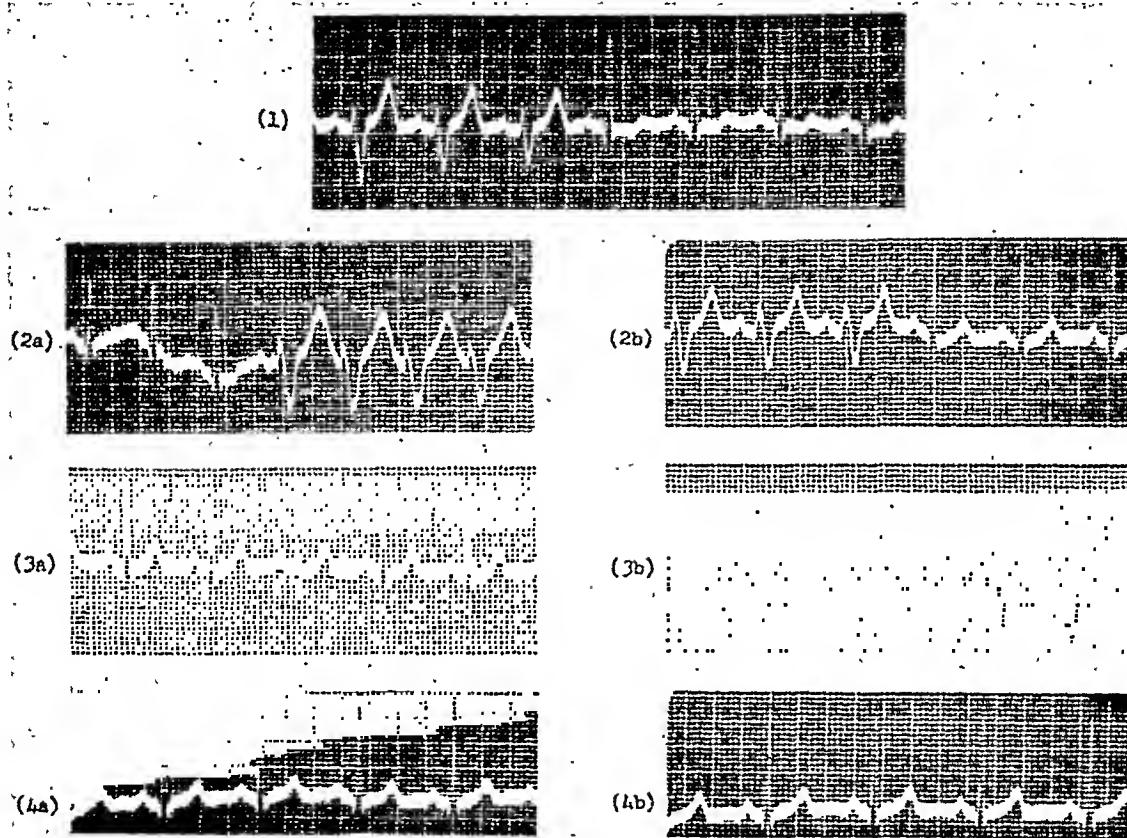


Fig. 2.—R. F. W., aged 29 years. Intermittent bundle branch block (Lead II). (1), Reversion to normal conduction when rate slowed following exercise. (2), After inhalation of amyl nitrite; interval between (2a) and (2b) about thirty seconds. (3a), Control; (3b), after 1/100 grain of atropine intravenously. (4a) Prostigmine followed by (4b) exercise; block did not develop.

Observations and Hospital Course.—Electrocardiograms taken before and after exercise showed that this patient had a normal intraventricular conduction time when the cardiac rate was relatively slow, but that he always developed bundle branch block when the rate increased above a critical level. The transition was invariably abrupt and the cycle marking the transition was of the same duration as the cycles preceding and following it.

By the use of the electrocardiograph and, later, the cardioscope it was found that the patient's subjective feeling of palpitation was usually a reliable indication of the presence of the bundle branch block. Although attacks of palpitation, and presumably block, occurred spontaneously, rarely was an electrocardiogram obtained during such spontaneous attacks. We therefore used various procedures to alter the heart rate so that the effect on the block of changes in rate could be studied.

Fig. 1 shows the appearance of block after the heart rate was increased by exercise.

Fig. 2 is a series of tracings all made on Lead II, which illustrate the effect of varia-

tion in rate induced in several ways. Fig. 2, (1), is a portion of tracing showing the transition from bundle branch block to normal conduction. The transition occurred as the heart rate was slowing following exercise. Fig. 2, (2a) and (2b), shows bundle branch block appearing after the inhalation of amyl nitrite. This tracing was a continuous one; a segment of thirty seconds' duration, between (2a) and (2b), was removed to facilitate illustration. Tracings (3a) and (3b) shown in Fig. 2 were taken before and after the intravenous injection of $\frac{1}{100}$ grain of atropine sulfate. This dose of atropine was not large enough to induce the block. The block appeared only after the patient assumed the upright position and hopped several times. Fig. 2, (4a), shows the effect of prostigmine. In this study the patient was given 1 c.c. of prostigmine methylsulfate 1:2,000 intramuscularly and was then exercised violently. Although he became dyspneic, his pulse rate did not increase markedly and bundle branch block did not develop.

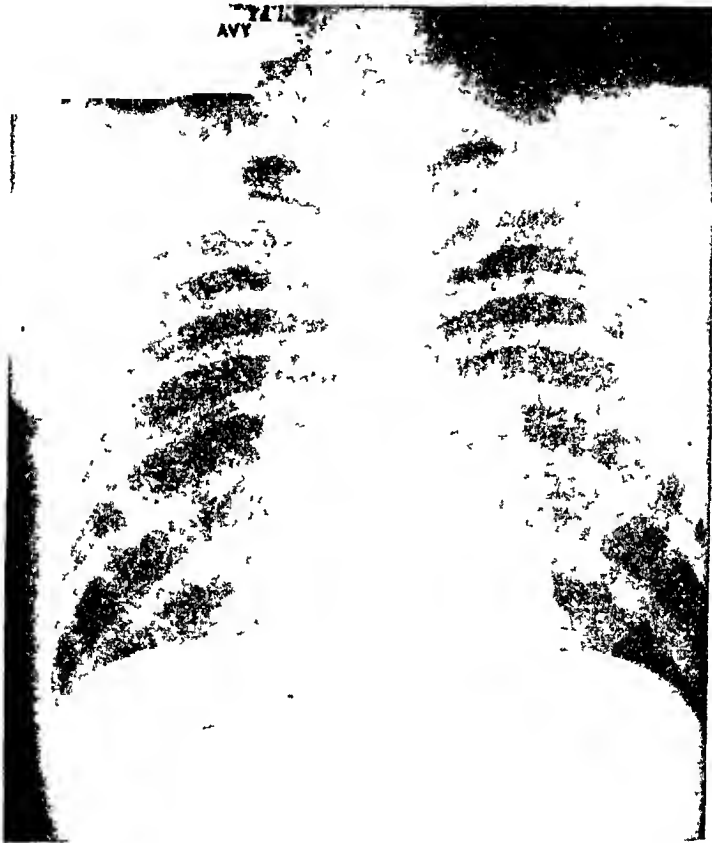


FIG. 3.

Several similar cases^{1, 3} have been reported in which either carotid sinus pressure or oxygen inhalation reduced the heart rate and caused bundle branch block to disappear. Since rapid heart rates could be maintained in this patient only under artificial conditions it was decided to attempt to maintain a high rate by atropine administration and then to observe the effects of oxygen and of carotid sinus pressure upon the block. Atropine sulfate, $\frac{1}{50}$ grain, administered intravenously, increased the rate to a point where the block occurred transiently, but it could not be maintained. However, when the patient stood erect, the rate rose to 136 per minute and the block appeared and persisted. He was then given 100 per cent oxygen inhalation for five minutes. There was neither marked slowing of the rate nor alteration in the degree of block. The application of carotid sinus pressure first on one side, then on the other, and finally bilaterally, was likewise ineffective in altering either the rate or the contour of the complexes.

Table I shows the observed variations in rate and the appearance of block under various conditions. Table II is a summary of all the observed variations in rates under different experimental conditions and of the rates at which bundle branch block was observed. The rate of 118 per minute, the average rate at which the transition from normal conduction to bundle branch block occurred, is the approximate "critical rate." It should be noted that occasionally a rate higher than the "critical rate" was necessary to induce the block. Also, the rate sometimes went below the critical level before the block disappeared.

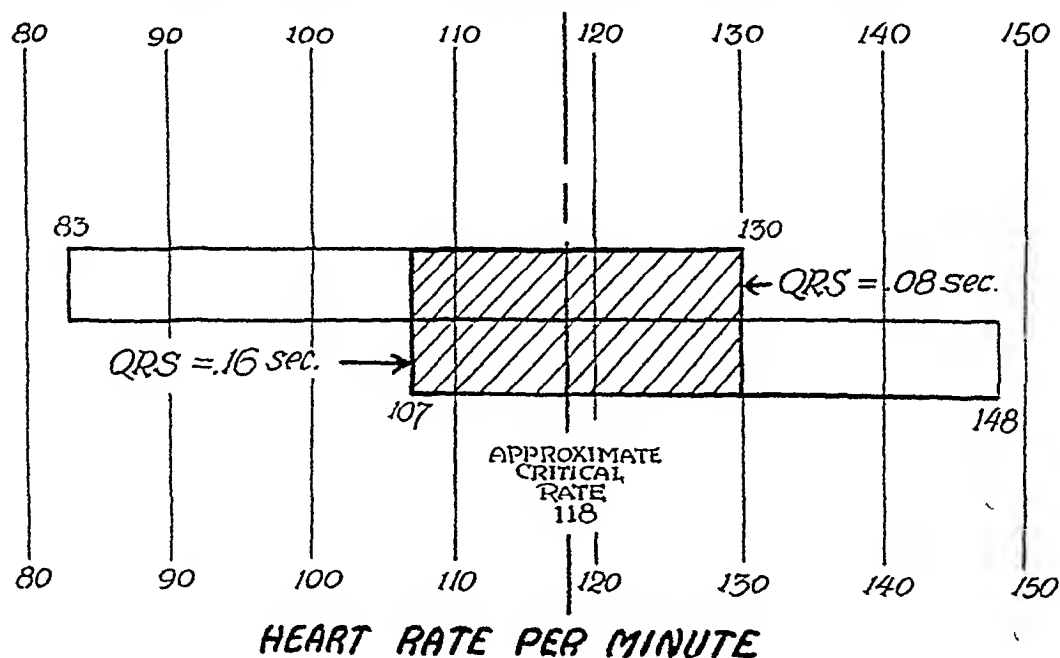
During the time spent in the hospital, the patient led a quiet existence devoid of strenuous physical activity. His attacks of palpitation became less frequent, and, at the time of his evacuation to a mainland hospital, he was feeling relatively well.

TABLE I. VARIATIONS IN RATE AND DEVELOPMENT OF BUNDLE BRANCH BLOCK UNDER VARIOUS EXPERIMENTAL PROCEDURES

PROCEDURE	0.08 SEC. MIN.-MAX.	0.16 SEC. MIN.-MAX.
Resting	83-100	107-115
Immediately after exercise		107-126
Two minutes after 2-step exercise	83- 85	
Atropine sulfate, $\frac{1}{100}$ grain intravenously	107-110	
Atropine, $\frac{1}{100}$ grain and light exercise		107-146
Atropine, $\frac{1}{100}$ grain patient standing		135-148
Atropine, $\frac{1}{100}$ grain patient bending over	92- 96	
Amyl nitrite inhalation	98-130	107-136
Carotid sinus pressure bilateral, patient reclining	84- 86	
Adrenalin, 1 c.c. intramuscularly	90-112	

TABLE II.

VARIATIONS IN RATES UNDER ALL CONDITIONS ~ SUMMATION



DISCUSSION

The lability of the cardiac conduction mechanism in this case offered an unusual opportunity to observe the function of the heart during periods of normal and prolonged intraventricular conduction time. Such observations

have a possible bearing on the existing concepts of the etiology and mechanism of bundle branch block.

The preponderant opinion concerning the etiology of bundle branch block is expressed in the literature by the statements that "bundle branch block is a manifestation of advanced cardiovascular disease" and that the "electrocardiographic changes must be attributed to anoxemia of the conducting tissues."¹ In most of the cases of bundle branch block in which the etiological factors could be established, the patients were found to have hypertensive or arteriosclerotic coronary artery disease.⁴ In such cases it is believed that an arteriosclerotic narrowing of a coronary artery branch supplying the bundle results in anoxia, with eventual fibrosis. As one would expect, most persons who have bundle branch block are in the higher age groups. The youngest case in the series reported by Comeau and his co-workers¹ was found in a patient 38 years of age.

The subject of this report experienced his first symptoms at 26 years of age. Our investigations revealed none of the usual stigmata of hypertensive or arteriosclerotic cardiovascular disease. All blood pressure readings as well as the renal function tests were within normal limits. There was no evidence of the existence of cardiac insufficiency or failure. In spite of the development of bundle branch block during the test, the exercise tolerance was good. Observation of the fundal vessels and palpation of the peripheral vessels showed the arteries to be normal.

In one of the cases cited³ the administration of oxygen during a period of bundle branch block caused the QRS to revert to normal. This response to oxygen therapy was considered to support the concept that the block was caused by anoxia of the bundle. Administration of oxygen to our patient during a period of bundle branch block had no observable effect. In several other cases cited in substantiation of the anoxia theory of bundle branch block, the inhalation of amyl nitrite caused the block to disappear. In our case the inhalation of amyl nitrite invariably brought about bundle branch block whenever the "critical rate" was exceeded.

Other diseases have been mentioned as etiological factors in the occurrence of bundle branch block. These include chronic rheumatic heart diseases and acute infections, neither of which could be demonstrated in our patient.

Vagal influences are known to produce varying degrees of block of the S-A or A-V node. Stimulation of vagus reflexes by carotid sinus pressure had no apparent effect on cardiac conduction in this subject. On the contrary, increase in vagal tone brought about by the administration of prostigmine prevented the development of block by its depressant effect on the cardiac rate.

Congenital defects of the conduction system have been mentioned as possible causes of similar abnormalities. None of the features of this case enabled us to establish this possibility.

A case cited by Graybiel and his co-workers⁸ had more features in common with this case than any other case reviewed. Their patient, a 24-year-old "healthy" aviator, developed transient bundle branch block as a result of a

fright stimulus. The firing of a pistol close to him caused the block to develop; it persisted for about two days. From their observations in that case and in others among young men in whom the QRS duration was abnormally prolonged, the authors suggested that "possibly all the disturbances of intraventricular conduction need not be explained on an anatomic basis."

Many controversial theories have recently been offered to explain the mechanism of bundle branch block. During the investigation of our case, we were able to test the validity of some of these theories by determining whether or not they conformed to the conditions that follow. We obtained many graphic records of the transition between normal conduction and bundle branch block. The following characteristics were repeatedly recorded: (1) Bundle branch block always occurred when the cardiac rate exceeded a certain level, and the duration of the QRS complex always became normal when the rate decreased to normal levels. (2) Any stimulus which caused the rate to increase sufficiently produced the block. (3) The transition always occurred abruptly: the cycle in which the first bundle branch block complex appeared approximated the lengths of the cycles occurring immediately before and after the transition cycle. (4) The increase or decrease in the QRS duration was not gradual, but occurred instantly during the transition cycle. (5) There was an immediate reversal of axis deviation at the time the block occurred. (6) During the period of observation, the block showed no tendency to become permanent.

Comeau and his co-workers¹ explain the abrupt changes of the QRS complexes in transient bundle branch block by assuming that conduction in the bundle is not completely blocked but simply depressed. Under such conditions, an increase in the frequency of the impulses transmitted results in an increase in the degree of conduction depression, until at the critical level an impulse traveling the roundabout way through the intact side and the myocardium reaches the affected ventricle before the impulse descending through the depressed branch is able to do so. The slow impulse reaches the ventricle too late to participate in its activation and is as ineffective as an impulse which is completely blocked. Thus small changes "such as an increase or decrease in diastolic rest due to alterations in heart rate" might produce the abrupt changes in the form of the complexes.

This concept, however, fails to consider the possibility that at the approximate critical rate, two impulses might reach different points of the affected ventricle at the same instant. This could occur if one impulse reaches the affected ventricle by traversing the normally functioning bundle branch while the impulse passed through the depressed bundle. Until one impulse comes to reach the ventricle sufficiently early to completely overshadow the effect of the slower impulse, one would expect to find records showing complexes of an intermediate form. Such complexes were recorded in a case of bundle branch block reported by Miller and Fulton.² In that case, several electrocardiographic records showed gradual alterations of the normal complexes which resulted eventually in the typical bundle branch complex. In the case herein reported intermediate complexes were never noted.

This hypothesis of depressed conduction through the bundle branch system has been weakened further by recent studies of the cardiac conduction system. Glomset, Glomset, and Birge,⁵ after painstaking study, were unable to demonstrate a readily recognizable and anatomically distinct ventricular conduction system. Failing to find a specific conduction system, they postulated that bundle branch block complexes are a result of unilateral ventricular strain, or unilateral coronary insufficiency, or a combination of the two. This concept is somewhat in accord with that of Master, Kalter, Dack, and Jaffe,⁶ who believe that the bundle branch complex results from a disproportionate enlargement of one or the other ventricle. Since ventricular strain and enlargement develop gradually, the contour of the QRS complex in transient bundle branch block would be expected to change gradually if bundle branch block is the result of these changes.

These hypotheses therefore seem unsatisfactory explanations of the abrupt changes in the QRS complexes noted in this and other similar cases. It would appear that a better explanation of the change of the QRS complex in transient bundle branch block must await the results of further investigation.

SUMMARY

1. An unusual case of transient bundle branch block is presented in which normal QRS complexes were present at slow cardiac rates and bundle branch block appeared at higher rates; this alteration occurred whenever the rate was varied sufficiently.

2. No demonstrable evidence of organic heart disease could be found to account for the transient block.

3. Theories of etiology and the mechanics of bundle branch block are discussed in relationship to this case.

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Abstracts and Reviews

Selected Abstracts

Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects. Bull. New York Acad. Med. 22: 57 (Feb.) 1946.

The subject of congenital cardiovascular defects in which surgical treatment has been effective is presented as the Harvey Lecture. The author reports his experiences with operative procedures in the treatment of patent ductus arteriosus, coarctation of the aorta, and pulmonary stenosis and atresia. The operation for pulmonary stenosis and atresia is of particular interest. As recently performed, it usually consists of anastomosis of the right subclavian artery and the pulmonary artery. The left subclavian artery is seldom used because considerable kinking of the vessel occurs when the anastomosis is made. In infants and small children, the innominate artery should be used. Another consideration in the choice of which artery to use is the occurrence of a right rather than a normal left aortic arch. When the aorta descends on the right, the innominate artery is directed to the left and must be approached through the left side of the chest. There have been 16 patients of this type in the author's series. The correct diagnosis was made before operation by fluoroscopic examination in which deviation of the barium-filled esophagus was seen.

The author stresses the importance of making a direct measurement of the pressure in the pulmonary artery when the vessel is exposed preparatory to the anastomosis. In most of his patients the pulmonary arterial pressure was approximately 175 mm. of water. In one patient who had a pressure of 310 mm. of water, the operation was performed but the cyanosis did not disappear and death occurred on the twenty-fourth postoperative day. At autopsy, a single ventricle was found, from which both the aorta and the pulmonary artery arose. There was little if any pulmonary stenosis. The cyanosis in this case was due to complete absence of a ventricular septum. It was obvious that the anastomosis should not have been performed. Recognition of the high pressure in the pulmonary artery should have furnished the clue to the true nature of the condition.

There was no significant impairment of the circulation in the arm when the subclavian artery was divided and used for the anastomosis. Although the skin temperature of the limb on the operated side was slightly cooler, motion and sensation were little, if at all, affected.

Either the right or left subclavian was used for the anastomosis in 26 patients. In 23 additional patients the innominate artery was used and in each instance it was necessary to ligate the first portion of the subclavian artery. The first portion of the right or left subclavian artery was therefore ligated in 49 cases, and in none of these was there any evidence of dangerous interference with the circulation of the arm. Seven patients died. In two of the seven patients the preoperative diagnosis was incorrect. In two of the remaining five cases death was attributed to cerebral ischemia or thrombosis.

The author's results up to Nov. 1, 1945, are summarized as follows: Fifty-seven operations have been performed on 55 patients. Ten of these patients have died. In this group the preoperative diagnosis, tetralogy of Fallot, was proved by autopsy to be in error in two instances. If these two cases in which the diagnosis was incorrect are excluded, there were eight deaths among the remaining 50 patients, a mortality of 16 per cent. In 40 of the living patients, improvement has been conspicuous. The condition of most of the children has been altered from invalidism to apparent if not real normality. The cyanosis has largely disappeared, even after moderate effort. The clubbing of fingers has either disappeared or con-

siderably diminished. The average oxygen saturation of arterial blood has risen from 49 per cent prior to operation to 79 per cent two to three weeks after operation.

It is emphasized that the operation is not of value to all patients who have persistent cyanosis. It is indicated only in those malformations in which the cardinal difficulty is lack of adequate circulation to the lungs.

BELLETT.

Silver, S. L., and Baker, L. A.: Reexamination of Veterans Discharged Because of Heart Disease or Hypertension. *J. A. M. A.* 130: 136 (Jan. 19) 1946.

Five hundred World War II veterans who had been discharged from the Armed Services because of diagnoses referable to the cardiovascular system, were re-examined and their medical records were reviewed. In 111 cases, the diagnosis of cardiovascular disease for which the patient received his certificate of disability discharge was not confirmed. In the remaining 389 patients whose diagnoses were confirmed, rheumatic heart disease had the highest frequency with an incidence of 169 cases (43.4 per cent). Of this group the mitral valve was involved in 82.6 per cent, the aortic valve was involved in 40.8 per cent, and mitral stenosis was present in 47.3 per cent. Arterial hypertension was the second most common diagnosis and occurred in 86 (27.5 per cent) of the patients. Thirty-three patients had been discharged because of coronary disease and of these, 21 patients had acute myocardial infarction. Congenital and syphilitic cardiovascular diseases were rare.

In 46 of the patients who had cardiovascular disease, no definite etiological factor could be established. The authors noted a conspicuous tendency for the signs of neurocirculatory asthenia and hypertension to disappear following return to civilian environment, indicating that poor psychological adjustment to military life had been responsible for the transient clinical manifestations. In about 40 per cent of this series there was a history of an etiological factor, or symptoms referable to the heart, or abnormal physical findings, which antedated entry into the service. It is pointed out that a more careful history and examination might have eliminated this group before induction.

BELLETT.

Logue, R. B., and Mullins, F.: Polyarteritis Nodosa: Report of 11 Cases With Review of Recent Literature. *Ann. Int. Med.* 24: 11 (Jan.) 1946.

The authors report 11 cases of polyarteritis nodosa diagnosed during life and review 177 cases reported in the English literature up to 1942. Polyarteritis nodosa affects men more frequently than women; in the authors' series there were 10 men and 1 woman. The ages of the patients ranged from 15 to 65 years. The duration of the illness varied from two and one-half months to one year, with recovery in one patient, who was well two years after onset of the disease. Hypertension was present in every patient at some time during the course of the disease. Leucocytosis occurred in all patients and eosinophilia was present in five patients. In three cases the diagnosis was made by laparotomy. One patient developed a perirenal hemorrhage, and nephrectomy was performed because of a suspected neoplasm. Four patients had clinical and pathologic manifestations of involvement of the coronary arteries with progressive electrocardiographic evidence of coronary insufficiency. Three patients showed clinical or pathologic evidence of involvement of the testicular arteries.

NAIDE.

Russi, S., Blumenthal, H. T., and Gray, S. H.: Small Adenomas of the Adrenal Cortex in Hypertension and Diabetes. *Arch. Int. Med.* 76: 284 (Nov.-Dec.) 1945.

The incidence of benign adenomas of the adrenal cortex in 9,000 routine autopsies was found to be at least 1.45 per cent. The incidence was 2 per cent in women and 1.2 per cent in men. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general autopsy group, and both diseases were frequently present in association with such a tumor in a single person.

The authors discuss the relation of the adrenal hormones to diabetes and hypertension. In relation to hypertension the authors believe that there is a direct effect of the cortical hormones on vascular tone, the hormones rendering a person more sensitive to renin.

NAIDE.

Naide, M., and Sayen, A.: Venospasm: Its Part in Producing the Clinical Picture of Raynaud's Disease. *Arch. Int. Med.* 77: 16 (Jan.) 1946.

Observation of 10 patients with Raynaud's disease and four patients with Raynaud's phenomenon has disclosed evidence that spasm of the veins as well as of the arteries is present in the majority of these patients. Arterial spasm alone cannot explain the clinical picture in most patients. In some patients venospasm may predominate over arterial spasm. The clinical features vary in each patient depending on which part of the vascular tree is predominantly involved in the abnormal vasoconstriction. It is suggested that in some patients with Raynaud's disease the clinical picture is influenced by an anatomic disproportion in capacity between arterial and venous flow. On the basis of clinical observations of these patients during the test for basal vascular tone, a classification has been made to clarify the terms Raynaud's disease and Raynaud's phenomenon. Raynaud's disease is not rare. The milder forms are fairly common and do not deserve the serious connotation usually associated with the diagnosis. Reassurance is an important part of treatment. A patient with so-called "cold allergy" was found to develop venospasm on exposure to cold without developing arterial constriction, which explained the development of cyanosis and marked swelling without blanching.

AUTHORS.

Peet, M. M., and Isberg, E. M.: The Surgical Treatment of Arterial Hypertension. *J. A. M. A.* 130: 467 (Feb. 23) 1946.

Since the first bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy was performed by Peet in 1933, more than 1,500 patients with essential hypertension have received this treatment at the Hospital of the University of Michigan. The authors report the results of this treatment in 437 patients followed for five to twelve years. Two hundred and fifty-one patients, or 57.5 per cent of the series, were living five to eleven years after operation. At the end of five postoperative years 64.8 per cent of the entire series were alive. The hypertensive state in 82 per cent of the patients in this series had already progressed to serious organic disease prior to operation. Fifty-six per cent of all the men had died, while the mortality among the women was only 30 per cent. Ninety-five per cent of hypertensive patients who showed no preoperative evidence of cardiac, cerebrovascular, or renal involvement were living five to eleven years after operation.

Approximately one-third of all patients who manifested preoperative evidence of organic heart disease, cerebrovascular disease, or impaired kidney function did not survive five to eleven years. Nineteen per cent of 112 patients with preoperative malignant hypertension were living five to eleven years later.

Fifty-one patients had maintained normal blood pressure levels and 28 showed no evidence whatever of hypertensive disease five to eleven years after operation. Significant reductions in blood pressure, complete and definite symptomatic relief, improvement of eye grounds, and improvement of abnormal electrocardiograms, cardiac enlargement, and kidney concentrating ability had been maintained for five to eleven postoperative years in a remarkable percentage of patients. Sixty per cent of patients who had previous cerebral accidents suffered no recurrence during the long postoperative period.

Surgical treatment is a measure to be considered in the management of every case of essential hypertension but to be utilized only when indicated. Evidence of progression and activity of hypertensive disease constitutes indication for surgical treatment.

NAIDE.

Loewe, L., Rosenblatt, P., and Hirsch, E.: Venous Thromboembolic Disease. *J. A. M. A.* 130: 386 (Feb. 16) 1946.

One hundred and twenty-five cases of thrombophlebitis and/or phlebothrombosis treated by the subcutaneous administration of heparin in the Pitkin menstruum are reported. Pitkin's menstruum consists of 18 per cent gelatin, 8 per cent dextrose, 0.5 per cent glacial acetic acid, and sufficient distilled water to make 100 per cent. Each ampule contains 200

mg. of heparin/Pitkin menstruum. The average patient can be kept heparinized by the administration of 300 mg. every second day. The usual period of treatment for the average case of thrombophlebitis is ten days to two weeks.

The treatment of venous thromboembolic disease with subcutaneous heparin in this manner was attended with lessened morbidity, prompt and rapid clinical improvement, and little or no residual edema. Treatment failures with other methods have subsequently ended in recovery following the routine administration of heparin in the Pitkin menstruum. The authors recommend this method of treating venous thromboembolic disease as being safe, simple, practical, and effective.

NAIDE.

Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis. *J. A. M. A.* 130: 398 (Feb. 16) 1946.

The authors studied the use of dicumarol as an anticoagulant in 110 patients with coronary thrombosis and myocardial infarction. Sixty patients received the usual treatment, while 50 received in addition dicumarol sufficient to maintain their plasma prothrombin activity at 35 to 50 per cent of normal. It was noted that three of every four cases of coronary thrombosis exhibited an increased prothrombin activity with increased clotting tendency. In view of this increased clotting tendency and due to the formation of mural thrombi and the danger of emboli, the anticoagulant seemed indicated to prevent the occurrence of such complications. It is also suggested that the administration of adequate amounts of an anticoagulant may prevent extension of the thrombus and reduce chances of future formation of mural thrombi or venous thromboses in the lower part of the body.

Dicumarol was administered to the 50 patients with coronary occlusion throughout their hospital course, which averaged forty-two days. Aside from a mild diarrhea and occasional nausea or headaches, no toxic effects were observed. No case of frank hemorrhage and no deaths ascribable to dicumarol occurred in this series. It was noted that the sedimentation time was increased by the drug to such an extent that it no longer served as an index of healing in the damaged myocardium.

Contraindications to dicumarol administration include renal disease, evident hepatic disease, or a blood dyscrasia with hemorrhagic tendencies. Patients with definite hypertension must be carefully observed from the standpoint of regulation of dosage.

The incidence of clinical embolism was 16 per cent in the group not receiving dicumarol and 2 per cent in the dicumarolized group. The mortality rate was 20 per cent in the nondicumarolized group and 4 per cent in the dicumarolized group. There was no evidence of more rapid healing of the infarction as judged by the electrocardiograms of the two groups.

In view of the recent reports that digitalis tends to increase the tendency toward coagulation the authors particularly advocate the use of dicumarol in patients with coronary thrombosis who are receiving digitalis.

In view of the encouraging results, it is suggested that further clinical evaluation of dicumarol is warranted.

BELLETT.

Spain, D. M., and Handler, B. J.: Chronic Cor Pulmonale. *Arch. Int. Med.* 77: 1 (Jan.) 1946.

The subject of chronic cor pulmonale is discussed from the standpoint of incidence, etiology, pathogenesis, clinical picture, diagnosis, clinical course, and treatment. This report is based upon a series of 60 consecutive cases of cor pulmonale studied at necropsy. Those cases were selected in which there was no significant evidence of hypertension, valvular heart disease, congenital lesion, syphilitic cardiovascular disease, or coronary atherosclerosis and at necropsy the wall of the right ventricle was found to be hypertrophied to a greater degree than that of the left ventricle. The following underlying pulmonary conditions were present in this series: emphysema in 40 cases (66 per cent);

bronchiectasis and bronchial asthma, each in six cases; silicotuberculosis in three cases; pulmonary tuberculosis in two cases; and kyphoscoliosis, pulmonary arteriolarsclerosis, and organized pulmonary thrombi, each in one case. The role and method by which each of these conditions acts in producing cor pulmonale is discussed in detail.

The authors emphasize the common errors made clinically in the diagnosis of this condition. In about 50 per cent of the cases the common error was to denote arteriosclerotic heart disease. They emphasize the following points in making a correct diagnosis: careful observation of physical signs, increase in size of the heart toward the right, prominence of impulse in the epigastrium, accentuation of pulmonic second sounds, roentgenographic and fluoroscopic studies, and presence of right axis deviation in the electrocardiogram. Occasionally in the presence of congestive failure, murmurs appearing over the pulmonic area give rise to an erroneous diagnosis of rheumatic or congenital heart disease. BELLET.

Rosenberg, D. H.: Acute Myocarditis in Mumps (Epidemic Parotitis). *Arch. Int. Med.* 76: 257 (Nov.-Dec.) 1945.

Cardiac involvement in mumps has been previously considered rare. Rosenberg observed significant electrocardiographic evidence of myocardial involvement in 16 of 104 patients studied (15.4 per cent). The following electrocardiographic abnormalities were encountered: biphasic or inverted P waves in one or more leads, prolongation of the P-R interval, elevation of the S-T segment in CF₁, and inversion of the T waves. Alterations of the T waves were observed in all 16 patients and occurred with the same frequency in each of the four leads. In this series there were also two cases of high-grade A-V heart block; one complete, the other partial. In all but one patient, electrocardiographic abnormalities were observed between the fifth and tenth days of illness and, in the majority of patients, were present on the eighth or ninth days. Precordial pain, either alone or with dyspnea, and palpitation developed in four of the 16 patients.

The nature of the histopathologic changes in the myocardium has not been definitely determined. It is not certain whether they represent an acute interstitial myocarditis with infiltration of polymorphonuclear leucocytes, as reported in the single case of Manca, or other milder types of myocardial involvement. From the clinical course and electrocardiographic findings, it is suggested that the myocardial changes are usually mild and reversible. The author makes the additional point that since the parotid involvement in mumps is not infrequently slight, and often overlooked in spite of the other clinical manifestations of the disease, the presence of arthralgia in such cases, together with electrocardiographic changes, might lead to a mistaken diagnosis of rheumatic fever. These observations cast further doubt on the specificity of the delay in A-V conduction time in the diagnosis of rheumatic fever. BELLET.

del Solar, A., Dussailant, G., Brodsky, M., and Levy, M.: A Critical Study of the Medical Treatment of Arterial Hypertension. *Rev. méd. de Chile* 73: 293 (April) 1945.

A study was made of the effectiveness of various forms of medical treatment for hypertension. A series of 182 cooperative patients who had essential hypertension was observed over a period of several years. The patients were all ambulatory and their blood pressures averaged 160 to 220 mm., systolic, and 90 to 130 mm., diastolic. They were examined at intervals of one to two weeks under rigidly consistent circumstances. Each patient was given a placebo for several months. This was followed by administration of one of the active drugs to be tested, also for several months. Finally a terminal placebo was given. For each patient, a determination was made of the independent blood pressure, which was the average blood pressure for the period in which no active medication was taken.

The administration of placebos was accompanied by a significant fall of systolic pressure in relation to the independent blood pressure in 13.9 per cent \pm 3.2 and of diastolic pressure in 8.7 per cent \pm 2.6 of 115 cases. Symptoms were alleviated in 83 per cent. These effects were

apparently due solely to psychogenic factors. Potassium thiocyanate, administered to 26 patients, produced a significant fall of systolic pressure in relation to the independent blood pressure in $73.1 \text{ per cent} \pm 8.7$ and of the diastolic pressure in $69.2 \text{ per cent} \pm 9$. The difference between the effect of thiocyanate and that of the placebo was too great to have been due to chance and thiocyanate is thereby demonstrated conclusively to have a marked hypotensive action. Other drugs tested, however, including bismuth subnitrate, sodium nitrite, bromide-phenobarbital, potassium iodide, and diethylstilbestrol, were devoid of any demonstrable action in lowering blood pressure with respect to the independent pressure.

LAPLACE.

Warembourg, H., and Fontan, M.: Considerations of Cardiac Reaction to Right and Left Pneumothorax. *L'Echo Med. du Nord* 15: 685 (Dec.) 1944.

The cardiac reactions to pneumothorax were studied over a period of several years to determine whether there are any differences characteristic of one side as compared with the other.

Left-sided pneumothorax produced no special clinical reactions of the heart, and serious accidents were rare. The heart rate was occasionally accelerated but sometimes was slowed. Radiologically, the heart was shifted to the right. Termination of pneumothorax was often followed by functional disorders of the heart which were benign but troublesome and included precordial pain, palpitation, and tachycardia. Torsion of the heart was sometimes accompanied by a loud systolic murmur at the pulmonic area. The changes in the electrocardiogram following left-sided pneumothorax included right axis deviation (34 per cent), deep Q wave (29 per cent), and alteration of T waves (33 per cent).

Right-sided pneumothorax was accompanied by transient acceleration of heart rate and never by slowing. All of the significant arrhythmias which were encountered, such as extrasystoles and paroxysmal tachycardia occurred when pneumothorax was on the right. In general, however, right pneumothorax did not cause the functional disorders of pneumothorax on the left. Right axis deviation and deviation of the S-T intervals occurred more frequently with right than with left pneumothorax and a tendency to low voltage was often manifested.

LAPLACE.

Prinzmetal, M., and Borgman, H. C.: The Nature of the Circulatory Changes in Burn Shock. *Clin. Sc.* 5: 205, 1945.

When rats were burned at 100° C. for fifteen seconds, denervation did not change the mortality or survival time. The shock produced by this type of burn is not explained by the small volume of local fluid loss and must therefore be toxic (humoral) in origin. The degree of hemoconcentration did not indicate the severity of this type of shock since there was insufficient local fluid loss to cause a significant elevation of hemoglobin. In toxic burn shock the hemoglobin values may fall and anemia may occur due partly to transfer of fluid from the tissues into the blood vessels and probably also to retention of red blood cells in the capillaries.

The characteristics of toxic burn shock are demonstrated histologically to include an increase in the number of open capillaries and in the amount of blood retained in each capillary. The primary disturbance is capillary atony, visceral congestion, and diminution of bleeding volume which occur within one minute after burns. The vascular disturbance which prevents vascular contraction causes the organs of the exsanguinated shocked animals to remain congested while those of the exsanguinated normal animals become pale. Impairment of contractile power of the peripheral circulation in shock with consequent reduction in venous return, was demonstrated by the fact that the bleeding volume of animals without hearts was the same as those with hearts. A humoral agent in the blood of burned animals can be demonstrated by the reduction of the bleeding volume of normal animals after they have been injected with large amounts of blood from burned animals.

LAPLACE.

Lewis, T.: Congenital Tricuspid Stenosis. Clin. Sc. 5: 261, 1945.

A case of tricuspid stenosis in a newly born child is described. The macroscopic appearance was that of endocarditis, but on histologic examination it was found that the lesion was a congenital malformation. Valvular deformities discovered in early life are believed to be usually if not always the result of congenital malformation rather than endocarditis.

LAPLACE.

Pickering, G. W., and Sanderson, P. H.: Angina Pectoris and Tobacco. Clin. Sc. 5: 275, 1945.

Tobacco angina is regarded by the authors as rare in occurrence but important because of its implications that tobacco may cause constriction of the coronary arteries. Three cases are reported in which anginal pain was induced or aggravated by smoking. One of the patients was carefully studied with respect to the manner in which smoking produced the pain. When the patient smoked following the disappearance of pain produced by exercise, the pain reappeared. It reappeared, however, only if smoking was accompanied by an adequate increase in pulse rate. Exercise tolerance was not reduced by smoking before or during the exercise. Smoking was therefore a relatively minor factor in the production of anginal pain in this case, and it appeared to produce the pain by increasing the work of the heart rather than by causing vasoconstriction.

It is pointed out that use of the term "tobacco angina" is scarcely justifiable since smoking plays such a relatively small and inconsequential part in the production of anginal pain.

LAPLACE.

Eyster, J. A. E., and Gilson, W. E.: The Development and Contour of Cardiac Injury Potential. Am. J. Physiol. 145: 507 (Feb.) 1946.

By applying increasing increments of suction to a small region of heart muscle, the development of injury potentials of rest and activity has been observed. When completely developed, the injury potential curve of activity is fundamentally monophasic in form and consists of only two parts: (1) a part in which the resting potential, negative with respect to uninjured resting muscle, is rapidly abolished and replaced by a potential positive with respect to the same reference, and (2) a slower and continued decline of the potential to the resting state. Modifications in this curve causing it to depart from this strictly monophasic type may result from two factors, inclusion of action potentials from uninjured regions of the muscle and from incomplete or nonuniform injury. The former occur most prominently in bipolar leads, are less often present in unipolar leads, and are usually absent in coaxial leads. The latter effects are prominent during the development of suction injuries or during their subsidence and are always, in our experience, present in injury potential curves derived from burned or crushed regions.

It is shown by several experimental methods that the injury potential of activity is derived solely from the region of injury or the immediately contiguous tissue. The electrode on uninjured tissue contributes to the recorded curve only by the addition of active potential components arising from the region of the electrode or from normal heart tissue intervening between the two electrodes.

AUTHORS.

Wintrobe, M. M.: Relation of Nutritional Deficiency to Cardiac Dysfunction. Arch. Int. Med. 76: 341 (Nov.-Dec.) 1945.

This article contains a good summary of the cardiac effects of nutritional deficiency. The author reviews the literature on the subject from the clinical and experimental standpoints and reports his own experiments upon the production of thiamine deficiency in pigs. The effects of avitaminoses, particularly of vitamin B₁, are discussed from the clinical, electrocardiographic, and pathologic standpoints.

BELLETT.

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ELECTROCARDIOGRAPHIC CHANGES IN PERICARDITIS ASSOCIATED WITH UREMIA

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ONE of the responsibilities of the present-day physician is that of caring for the patient who has uremia. More of these patients now are seeking medical advice, and the condition demands broader and more accurate knowledge than heretofore. During the last few years, closer observation of these patients in the hospital has led to the more frequent recognition of pericarditis.¹⁻⁶ Different investigators have suggested that serial electrocardiograms taken during the course of pericarditis^{7, 8} should give needed information in regard to typical abnormalities and that a more accurate appraisal of the significance of these abnormalities should be made.

The following report consists of clinical, chemical, serial electrocardiographic, and pathologic observations in three cases of severe chronic renal insufficiency in which recognizable pericarditis developed while the patients were under our care. These cases presented a unique opportunity for an intensive study of uremic pericarditis.

REPORT OF CASES

CASE 1.—The patient, a white youth, was 17 years of age when he first registered at the Mayo Clinic, Oct. 24, 1939, approximately four years before the terminal illness during which pericarditis developed. He had contracted measles and mumps in early childhood. He had undergone tonsillectomy when he was 3 years of age. At 7 years he had scarlet fever, from which he recovered completely. In March, 1939, when the patient was 17 years of age, he developed a septic sore throat with fever and remained in bed for four days. There had been no definite sequelae. In the family history no significant facts were found with regard to the patient's illness.

In September, 1939, edema of feet and legs and some puffiness of the eyelids developed insidiously, and gradually increased. Albuminuria, hematuria, and cylindruria were found

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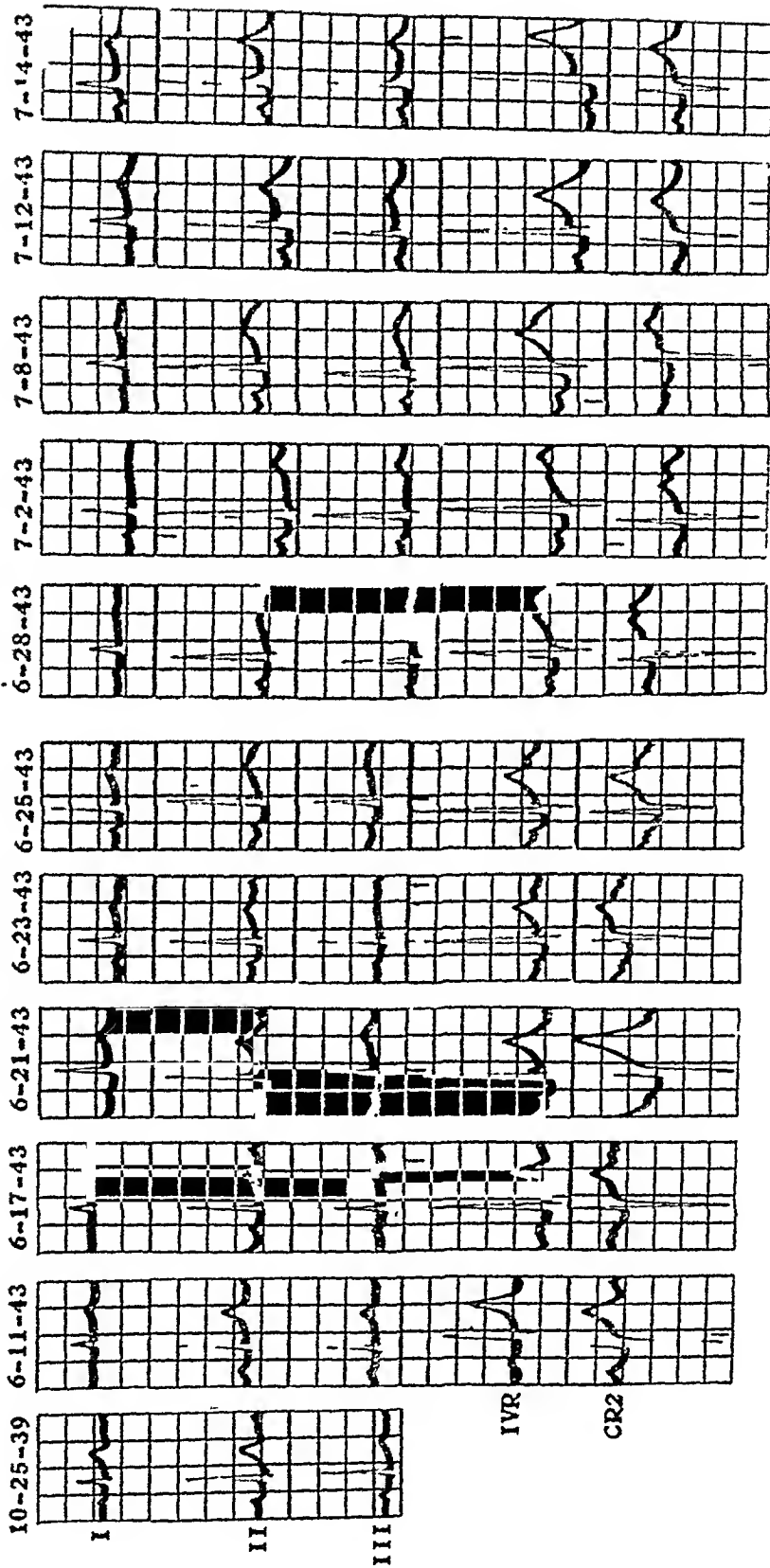


Fig. 1.—(Case 1.) In this series of electrocardiograms, changes of a type observed in pericarditis reach a maximum on June 21, regress, and then recur. They are still present in the last tracing taken before the patient's death.

on urinalysis at that time. The patient had been put to bed and in three weeks the edema had subsided although albuminuria persisted.

Physical examination on admission to the clinic on Oct. 24, 1939, revealed that the patient was 69½ inches (176.5 cm.) tall and weighed 146 pounds (66.2 kg.). There was slight edema of the eyelids and moderate edema of the dependent portions of the body. The lungs were clear, and there was no gross enlargement of the heart. With the ophthalmoscope a single small hemorrhage in the right retina was seen. The initial blood pressure was 170/90. Several routine urinalyses revealed albumin, Grade 3 to 4 (on a grading basis of 1 to 4, in which 1 represents the least amount and 4 represents the most amount); no reducing substances; some hyaline and granular casts; erythrocytes, Grade 2 to 3; and leucocytes, Grade 0 to 4. An electrocardiogram taken on October 25 revealed no significant variations from the normal (Fig. 1). Studies of the blood revealed mild secondary anemia, negative results of the flocculation test for syphilis, increased concentrations of urea (48 mg. per 100 c.c.) and cholesterol (287 mg.), and distinct hypoproteinemia (Table I). The standard urea clearance was reduced to 15 c.c. of blood cleared per minute. A diagnosis of early chronic glomerulonephritis was made and the patient was hospitalized. During the two weeks the patient was in the hospital the edema disappeared and he lost 17 pounds (7.7 kg.). Treatment consisted of a diet low in sodium chloride, which contained 2,000 calories and 80 Gm. of protein. The intake of fluids was limited to 1,500 c.c. per day. The diuretics, potassium nitrate, theobromine, and aminophylline, were given. Also 90 Gm. of acacia in a 6 per cent solution were injected intravenously.

The patient's second admission was on July 10, 1940. His general condition was good. The only abnormality was a trace of edema above both ankles. The blood pressure was 160/90. Urinalysis revealed findings similar to those on first admission. There was definite evidence of renal insufficiency; for example, the serum sulfate had increased to 7.3 mg. in 100 c.c. (Table I).

A year later, on Nov. 24, 1941, the patient returned to the clinic. He had attended school regularly in the interim. He had no edema, the blood pressure was 150/80, and the ophthalmoscopic findings in the retina were normal. The secondary anemia was more severe than on previous visits and renal insufficiency was more marked as evidenced by the standard urea clearance which was reduced to 6 cubic centimeters. Urinary findings were similar to those on previous visits. At this time the patient was given a transfusion of 500 c.c. of blood.

For the next year the patient had few untoward symptoms. However, during the winter of 1942 and 1943 the anemia became difficult to control and he was given nine transfusions of blood. His appetite became poor and in the six months before his last admission he occasionally vomited.

On the fourth and last admission, June 9, 1943, the patient was distinctly anemic. He was hospitalized at once. His breath had a uremic odor. The heart was not greatly enlarged. A soft systolic murmur was heard over the pulmonary region. However, there was no edema, and no retinitis was demonstrated on ophthalmoscopic examination. The blood pressure had risen to 175/115. Quantitative estimations of the protein in the urine revealed that the amount excreted varied from 1.14 to 1.93 Gm. in 100 c.c. of urine, and the total amount excreted in twenty-four hours varied from 3.5 to 16 grams. In spite of this considerable daily loss of protein in the urine, the serum protein and albumin fraction were at the lower limits of normal concentrations (Table I). Blood studies revealed distinct secondary anemia and marked azotemia. The concentration of blood urea was 342 mg. and of creatinine was 28 milligrams.

In the thirty-seven days the patient was under observation, the course was typical of terminal uremia secondary to chronic glomerulonephritis. Twenty-four hours after the patient was admitted to the hospital several general convulsions developed. Each was of short duration. Four days later, June 14, examination of the mouth revealed a white membranous exudate beneath the tongue, having the characteristics of so-called uremic frost. The next evening the patient had a general convulsion which lasted for ten minutes. On June 16, for the first time, a faint precordial to-and-fro friction rub was heard in the second left intercostal space. This rub was not heard thereafter until June 21 when a loud friction rub became

TABLE I. DATA ON BLOOD IN CASE 1

DATE	WHOLE BLOOD			BLOOD SERUM								BLOOD PLASMA			ECG
	HEMOGLOBIN (GM. IN 100 C.C.)	UREA (MG. IN 100 C.C.)	CREATININE (MG. IN 100 C.C.)	PROTEIN (GM. IN 100 C.C.)	ALBUMIN (GM. IN 100 C.C.)	ALBUMIN-GLOBULIN RATIO	SULFATE (MG. IN 100 C.C.)	CALCIUM (MG. IN 100 C.C.)	PHOSPHORUS (MG. IN 100 C.C.)	SODIUM (MG. IN 100 C.C.)	POTASSIUM (MG. IN 100 C.C.)	CHLORIDE (MG. IN 100 C.C.)	CARBON DIOXIDE COMBINING POWER (VOLUMES IN 100 C.C.)	CHOLESTEROL (MG. IN 100 C.C.)	
10/25/39	10.8	48		4.0	2.5	1.7/1						621	54	287	
10/26/39							5.1								
10/27/39															
10/30/39		38													
11/ 7/39		46													
7/20/40	11.6	42		4.4	2.8	1.7/1	7.3					617			
10/28/40	11.4	60		4.8	2.9	1.6/1	7.3								
11/25/41	8.9	122	6.4	5.2	3.4	1.9/1	9.7								
12/30/41	9.6	132	7.2												
1/ 2/42	11.6														
6/10/43	10.3	342	28	6.1	3.9	1.8/1	37	8.6	15		22.2		50		ECG 6-11
6/16/43		370	30												
6/17/43*		358	29						20	328	16.8		38		ECG
6/18/43								6.2			17.0		62		
6/21/43		380	34												
6/23/43		399	32								17.9		43		ECG
6/25/43	8.0	357	28								20.6				ECG
6/28/43		372	28								18.5		61		ECG
7/ 2/43		354	28								15.6				ECG
7/ 6/43		346	24					6.3	7	288	14.8		50		ECG
7/ 8/43*†	5.3	372	28						8		13.5		50		ECG
7/12/43‡	4.7	468	34	3.2	3.1	1.5/1	24	6.5	12.5	285	13.6		48	256	ECG
7/13/43		498	34				34		13		16.5		38		ECG
7/14/43		504	30								20.7				
7/15/43		558	34								21.6				
11:00 A.M.				47			61		17	279	23.6		43		ECG
2:55 P.M.									20	273			43		

Patient died

*Serum magnesium on June 17, 3.5 mg., and on July 8, 1.2 mg. in 100 c.c., respectively.

†Plasma cholesterol esters, 139 mg.; lecithin, 216 mg.; total fatty acids, 662 mg.; and total lipoids, 918 mg. in 100 cubic centimeters.

‡Blood culture: no growth in five days.

§Blood sugar, 106 mg. in 100 c.c.; blood uric acid, 14.8 mg. in 100 cubic centimeters.

audible and continued to be heard until June 24. Electrocardiographic tracings taken in the course of the first examination in October, 1939, and on June 11 and 17, 1943, in the first week of the last stay in the hospital, were not indicative of pericarditis (Fig. 1). However, on June 21, when the loud rub over the precordium developed, electrocardiographic tracings taken in the morning showed significant elevation of the RS-T segment in all three standard leads and in precordial Leads CR₂ and IVR. In the period from June 17 to 23, the patient's temperature rose each day to 99° F. or higher, and on June 18 it rose to 101° F. It is worthy of note that subsequently from June 25 to July 2 no pericardial friction rub was audible, the patient's temperature was normal, and the electrocardiographic changes diminished in magnitude. In the tracing taken on June 28 the RS-T segments were isoelectric in all leads except in Lead CR₂. The amplitude of the T waves especially in the standard leads was low in comparison to the height of this deflection in electrocardiograms taken prior to the episode of pericarditis (Fig. 1).



Fig. 2.—(Case 1.) Sanguinofibrinous pericarditis with fibrous adhesions.

On July 8, the friction rub recurred and persisted until the patient died on July 15. A culture of the blood taken on July 8 failed to show any growth over a period of five days. From July 9 to 15, inclusive, the patient's temperature rose to as much as 100.2° F. In the electrocardiogram made on July 8, elevation of the RS-T segment reappeared in the standard leads and precordial Lead IVR. Throughout the last seven days of the patient's life the friction rub was detectable and in electrocardiograms taken in this period the RS-T segment remained elevated (Fig. 1).

It is of interest that, in spite of the extreme grade of renal impairment, oliguria developed only during the last few days of life. The continued excretion of a considerable volume of urine was at least partly due to the intravenous injection of glucose solutions.

Blood was withdrawn from the vein of the arm of the patient on July 8 and analyses of the concentration of several ions in the plasma and serum were made. The results given in Table II reveal a low total ionic concentration and a preponderance of basic ions. These findings, in addition to carbon dioxide combining power in the plasma of 48 volumes per cent, support the viewpoint that even in marked chronic azotemia, as it occurred in this patient, acidosis need not necessarily be continually present.

On July 15 bilateral parotitis was present. The patient periodically lapsed into a semicomatose condition and died at 2:55 P.M.

Necropsy.—There was moderate emaciation. Two decubital ulcers, each 1 cm. in diameter, were present on the right buttock. There were 200 c.c. of blood-tinged fluid in the peritoneal cavity. The pericardial sac measured 15 cm. transversely and contained approximately 200 c.c. of bloody fluid. The epicardium and inner surfaces of the pericardial sac were covered by a thick hemorrhagic exudate (Fig. 2).

The heart weighed 330 grams (normal, 265 grams). A few dense fibrinous adhesions extended from the epicardium to the pericardial surface.

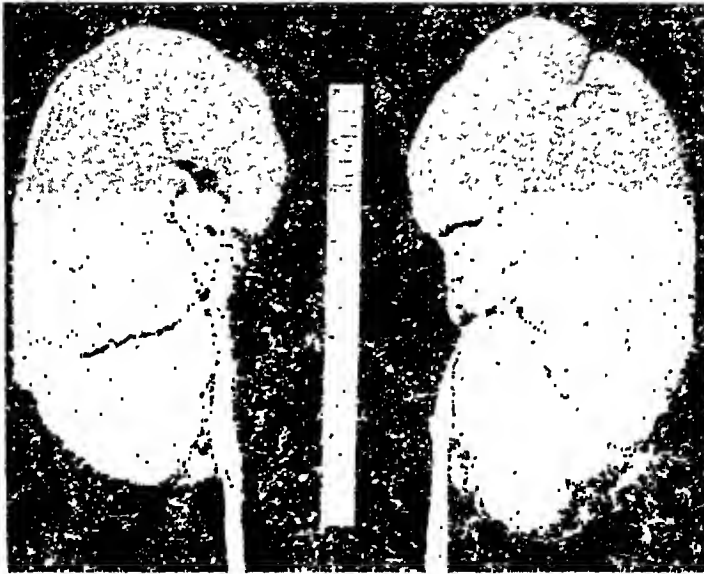


Fig. 3.—(Case 1.) Chronic glomerulonephritis with atrophy of the left kidney.



Fig. 4.—(Case 1.) Pericarditis. Note organization of the fibrinous exudate at the left (hematoxylin and eosin, $\times 120$).

there were scattered cotton-wool exudates and hemorrhages. The retinal findings were those of an acute angiospastic retinitis. Twenty routine urinalyses revealed albumin, Grade 2 to 4, and no reducing substances. In the sediment, erythrocytes and leucocytes, Grade 1, were found periodically. The finding of casts was not recorded. An accurate quantitative estimation of protein revealed 0.3 Gm. in 100 c.c. of urine. Blood studies indicated secondary anemia (hemoglobin, 9.1 Gm. in 100 c.c.); erythrocytes 3,100,000 per cubic millimeter, and leucocytes 4,300. The result of the flocculation test on the serum was negative for syphilis. The blood urea was 238 mg. and the serum sulfate was 26.3 mg. in 100 c.c. (Table III). These levels are indicative of severe azotemia. A roentgenogram of the thorax showed an enlarged heart shadow and a small effusion in the right pleural cavity. An electrocardiogram taken on January 12 showed nothing diagnostic of pericarditis or myocardial disease (Fig. 6).

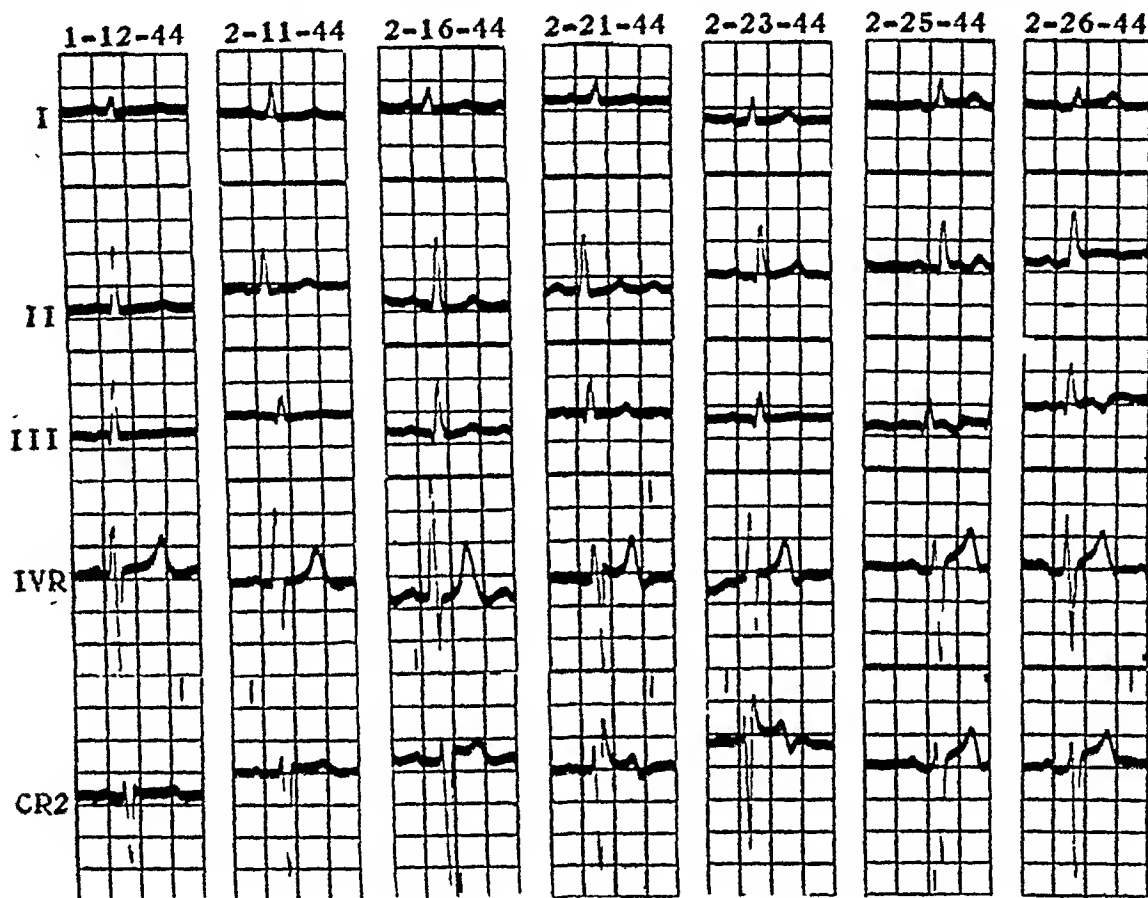


Fig. 6.—(Case 2.) Changes of a type observed in pericarditis never were present in more than minimal degree in this series of electrocardiograms. In the tracing taken on February 16, the RS-T segment in precordial Lead CR₂ is slightly elevated. Changes in this lead attain their greatest degree on February 23. Slight elevation of the RS-T segments in the standard leads appeared in the electrocardiogram on the same day and persisted throughout the remaining tracings.

The course of the patient's illness from Jan. 11 to Feb. 27, 1944, was typical of the terminal uremic state seen in chronic diffuse nephritis. The blood urea and creatinine gradually rose to 564 mg. and 23.5 mg. in 100 c.c., respectively, and the carbon dioxide combining power of the plasma decreased to 24 volumes per cent. Distinct oliguria did not develop until the last four days of the patient's life. From January 11 to February 11, the patient's condition changed little and at times she was fairly comfortable. Treatment included intravenous injections of glucose solutions and a transfusion of 500 c.c. of blood on January 26. On February 11, a few moist râles were audible over the bases of the lungs, but no change occurred in the region over the heart. The electrocardiogram was unchanged from that taken on January 12 (Fig. 6). On February 15, the patient became mildly confused and had some hallucinations. At times during the next day, February 16, twitching movements of the ex-

TABLE II. DISTRIBUTION OF ELECTROLYTES IN BLOOD PLASMA AND SERUM IN CASE 1*

BASE	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.	ACID	MG. IN 100 C.C.	MEQ. IN 1,000 C.C.
Sodium	285	124	Chlorides†	198	56.4
Potassium	13.6	3.5	Bicarbonate	48‡	21.5
Calcium	6.5	3.2	Protein	5.2§	12.5
Magnesium	1.2	1.0	Sulfates	24	5.0
Total Meq.		131.7	Phosphates	12.5	8.0
			Total Meq.		103.4

*Blood withdrawn July 8, 1943.

†Chlorides estimated as chloride.

‡Bicarbonate estimated from carbon dioxide combining power.

§Gram in 100 c.c. of serum. Base milliequivalents per liter bound by protein = 0.243 times grams of protein per liter.

In sections of the right lower lobe of the lung the alveoli were filled with serum and fibrinopurulent exudate.

In sections of the kidneys no normal glomeruli could be observed. About 60 per cent of the glomeruli were fibrotic, hyalinized, and obviously functionless structures. The remaining glomeruli revealed evidence of injury of varying degrees. Many of them were hypertrophied. The most constant change was endothelial proliferation of the glomerular tufts. Most of the capillaries were partially or completely blocked by this abnormal accumulation of endothelial cells. In some of these glomeruli, hyaline globular structures were present in the peripheral portions of the tufts (Fig. 5, *a* and *b*). These hyaline structures were identical in appearance to the lesions described in the kidney in Kimmelstiel-Wilson disease (intercapillary glomerulosclerosis). Adhesions between the glomerular tuft and the capsule, and pericapsular fibrosis were other changes frequently observed. Most of the tubules were atrophied and collapsed. Collections of lymphocytes were present in the interstitial tissue. A few tubules were dilated and contained casts of acidophilic albuminous material and red blood cells.

The large arteries appeared normal. The arterioles revealed moderate hypertrophy of the media but rarely any intimal hyalinization.

The following diagnoses were made: (1) chronic glomerulonephritis with atrophy of the left kidney and uremia (clinical); (2) chronic fibrinohemorrhagic pericarditis; (3) hypertrophy of heart (hypertension), and (4) early bronchopneumonia in the lower lobe of the right lung.

CASE 2.—The patient, a married white woman, 35 years of age, was admitted to the Mayo Clinic on Jan. 11, 1944, and was hospitalized immediately. She was suffering from uremia presumably due to chronic glomerulonephritis. She complained chiefly of dyspnea, edema of the legs, nausea, and vomiting. The family history revealed that her mother had Bright's disease and that one brother had high blood pressure. The patient had been married for seventeen years and was the mother of two healthy children. She had scarlet fever at 4 years of age and she underwent tonsillectomy at the age of 12 years. During the patient's first pregnancy, when she was 18 years of age, albuminuria was found and this had persisted since that time. Three years before admission the urine contained casts, blood, and pus, in addition to albumin. Her systolic blood pressure was 190 millimeters. Six weeks before admission, dyspnea with cough, dependent edema, some blurring of vision, nausea, and vomiting developed. Her systolic blood pressure was found to be more than 200 millimeters.

On physical examination at the clinic, the patient was 66¼ inches (168.3 cm.) tall and weighed 113½ pounds (51.5 kg.), and the blood pressure was 240/140. She was anemic. Numerous moist râles were heard over the bases of the lungs. On percussion the heart was found to be slightly enlarged, measuring 2.5 by 12.5 centimeters. The second aortic sound was accentuated, but no murmurs or rubs were audible. The liver and spleen could be felt at the costal margin. There was edema, Grade 1, of the lower part of the legs. On ophthalmoscopic examination the retinas were anemic, the optic discs were edematous up to 1 diopter, and

tremities and signs of bilateral hydrothorax developed. Edema, Grade 3, of the lower part of the back was also present. An electrocardiogram showed an increase in the height of the T wave in Lead IVR and a sharpening of the apex of this wave; the RS-T segment in Lead CR₁ was slightly elevated (Fig. 6). The patient's temperature was normal from January 29 to February 18, with the exception of February 16 when it reached 99.4° F.; however, from February 18 to February 23, it rose to 100° to 100.6° F. On February 21, so-called uremic frost covered the patient's tongue and the mucous membrane of the oral cavity and, for the first time, a precordial friction rub was heard. The electrocardiogram on the same day revealed that elevation of the RS-T segment in Lead CR₁ had increased and a slight elevation of this segment had appeared in Lead IVR. The friction rub continued to be audible throughout the remaining six days of the patient's life. In the electrocardiogram taken on February 23 (Fig. 6), a slight elevation of the RS-T segment in Leads I and II had appeared, and this feature was retained in the subsequent tracings taken on February 25 and February 26. However, the segmental elevation in the precordial leads disappeared almost completely in the last two electrocardiograms of February 25 and 26 (Fig. 6). The patient gradually became weaker and more drowsy and, on February 26, her blood pressure fell to 130/60, and the carbon dioxide combining power of the plasma decreased to 24 volumes per cent, indicating definite acidosis. On February 27, the patient was very drowsy, her blood pressure fell to 90/50, her temperature fell to 97.4° F., and she died at 9:25 P.M.



Fig. 7.—(Case 2.) Fibrinopurulent pericarditis.

Necropsy.—The peritoneal cavity contained 1,000 c.c. of clear yellow fluid and each pleural cavity contained 1,500 cubic centimeters. The pericardial sac measured 14 cm. transversely and contained 250 c.c. of yellow fibrinopurulent exudate.

The heart weighed 403 grams (normal, 234 grams). The entire epicardium was covered by a shaggy fibrinopurulent exudate which varied in thickness and was most prominent at the apex on the anterior surface (Fig. 7). There was a subendocardial hemorrhage in the papillary muscle of the left ventricle. The coronary arteriosclerosis was Graded 1, and there were no thrombi.

TABLE III. DATA ON BLOOD IN CASE 2

DATE, 1914	WHOLE BLOOD			BLOOD SERUM				BLOOD PLASMA		ELECTRO- CARDIOGRAM
	HEMO- GLOBIN (Gm. in 100 c.c.)	UREA (mg. in 100 c.c.)	CREATININE (mg. in 100 c.c.)	POTASSIUM (mg. in 100 c.c.)	CALCIUM (mg. in 100 c.c.)	PHOS- PHORUS (mg. in 100 c.c.)	SULFATE (mg. in 100 c.c.)	CHLORIDE (mg. in 100 c.c.)	CARBON DIOXIDE COMBINING POWER (volumes in 100 c.c.)	
1/12	9.1	238					26.3			ECG
1/14		226	10.4	21.0				557	18	
1/18		216	11.0							
1/19		220	12.8				21.1			
1/28	9.6	204	13.4	25.4				514	37	ECG
2/2*		201	16.2	21.6	9.2	8.6		451	44	ECG
2/11		240	16.8	19.0		10.6	18.2	449	47	ECG
2/14†		236	16.2	16.8						ECG
2/16		272	18.3	20.6				102	38	ECG
2/18‡	8.1	366	19.6	23.9						ECG
2/21		426	23.2	22.9				162	24	ECG
2/23		492	23.0	24.1	7.8	16.6		453	27	ECG
2/25		561	23.5	25.6				155	24	ECG
2/26		Patient died								
2/27										

*Serum protein, 5.5 Gm. in 100 cubic centimeters.

†Serum sodium, 262 mg. in 100 cubic centimeters.

‡Serum protein, 4.9 Gm.; serum albumin, 3.6 Gm.; albumin-globulin ratio, 2.7/1.0; plasma cholesterol, 231 mg.; cholesterol esters, 160

mg.; lecithin, 262 mg.; total fatty acids, 136 mg.; total lipoids, 670 mg. in 100 cubic centimeters.

in the myocardium. Sections of the upper lobe of the left lung revealed a recent infarct. There was moderate fatty metamorphosis in the liver.

In sections of the kidneys most of the glomeruli were fibrotic, hyalinized structures which appeared completely functionless (Fig. 10, *a*). A few glomeruli appeared normal but were greatly hypertrophied. Others presented thickening of the basement membranes of the capillary loops and focal hyalinization. The tubules were for the most part severely atrophied and collapsed. A few tubules in association with fairly normal glomeruli were dilated and contained acidophilic hyaline casts. In some regions numbers of tremendously dilated tubules lined by flattened epithelium and filled with acidophilic hyaline casts could be observed (Fig. 10, *b*). No glomeruli were visible in these areas. In sections of the left kidney there was suppurative interstitial nephritis with small abscesses (Fig. 10, *c*). Some of the tubules contained a purulent exudate. The small arterioles of the kidney were the seat of severe hyaline intimal thickening. There was moderate medial hypertrophy of the larger arterioles and arteries. Collagenous intimal thickening and reduplication of the elastic lamina were also observed (Fig. 10, *b*).

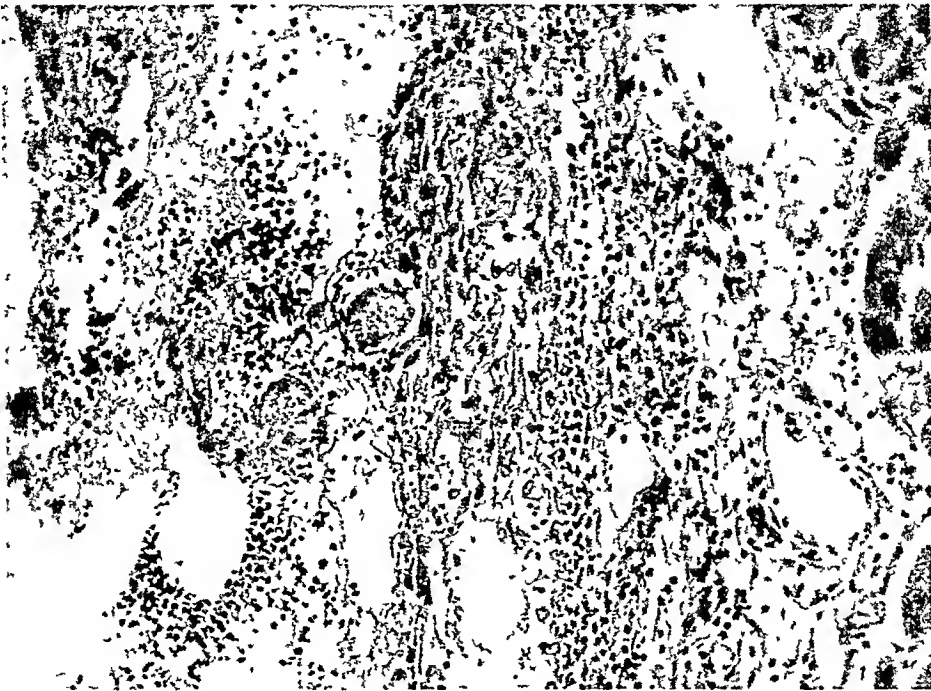


Fig. 9.—(Case 2.) Pericardium. Note organization of the fibrinopurulent exudate by fibroblasts (hematoxylin and eosin, $\times 140$).

Sections of the bladder revealed severe edema of the submucosa with the presence of many large mononuclear cells. In sections of the vagina there was evidence of recent thrombosis of small arteries with intense congestion of submucosa and ulceration of the epithelial surface.

The following diagnoses were made: (1) chronic pyelonephritis (interstitial nephritis) with atrophy of kidneys (total weight, 52 grams; normal, 234 grams) and uremia (clinical); (2) hypertrophy of heart (hypertension); (3) fibrinopurulent pericarditis; (4) bilateral hydrothorax and ascites; (5) infarct upper lobe of left lung; (6) bullous edema of bladder; and (7) ulcerative vaginitis and cervicitis.

CASE 3.—The patient, a white woman, was 37 years of age, a housewife, and mother of two healthy children when admitted to the Mayo Clinic. She was hospitalized immediately on Feb. 23, 1944. Nothing in the family history appeared to be significant with regard to her present illness. The important events in her past history were the development of urinary infection in the course of her first pregnancy in 1932; right tubal pregnancy for which right salpingectomy, together with appendectomy, was performed in 1939; pregnancy and cesarean

At the apex of the upper lobe of the left lung a brown wedge-shaped region of increased consistency measured approximately 2 by 2 cm.; it had the appearance of an infarct. Aside from severe atelectasis of the lower lobes of both lungs, no other lesions were observed in the lungs.

The right kidney measured 6 by 3.5 by 2 cm. and weighed 28 grams. The capsule was stripped with great difficulty from a granular and scarred surface. The cut surface was light brown and the markings were indistinct. The left kidney measured 6 by 3.5 by 1.5 cm. and weighed 24 grams. It had the same appearance as the right kidney (Fig. 8).



Fig. 8.—(Case 2.) Severe pyelonephritic atrophy of kidneys. Normal kidney below for comparison.

The mucosa of the bladder was congested moderately and there was severe bullous edema. The mucosa of the vagina was ulcerated and covered by a hemorrhagic purulent exudate which extended into the cervix. There were multiple small petechial hemorrhages on the surface of both ovaries.

Histologic Examination.—The parietal and visceral layers of the pericardium were covered by a fibrinous exudate which contained many polymorphonuclear cells and numerous colonies of microorganisms. These had the appearance of cocci. Numerous fibroblasts were growing into the fibrinous exudate from the epicardium (Fig. 9). No lesions were observed

section for placenta previa in April, 1943. The present illness began in October, 1943, with the development of migratory arthritic pains in several joints. Anemia was noticed by her physician. Later there were mild swelling of the joints of both hands, wrists, and elbows and a rise in body temperature. In November, the fever recurred and edema of ankles and legs appeared and persisted. In January, 1944, pitting edema became general and the patient's eyelids were affected. Afternoon fever up to 101° F. and sweating occurred. The urinary output diminished at this time and her physician found on urinalysis albuminuria and pyuria. The extent of edema fluctuated during February, but during the week before coming to the clinic it increased distinctly and the patient gained seven pounds (3.2 kg.). During that week the patient noticed pain in the left anterior part of the thorax and dyspnea on exertion. In the two to three months before admission she had on several occasions passed watery stools.

On physical examination the patient was 66½ inches (168.9 cm.) tall and weighed 120 pounds (54.4 kg.). She appeared to be slightly anemic. General edema, Grade 2, was present. The wrist and the joints of the right hand were swollen. The blood pressure was 125/75. Ophthalmoscopic examination revealed normal ocular fundi. Routine urinalyses revealed albumin, Grade 2 to 4, and no reducing substances. The sediment contained erythrocytes, Grade 0 to 2, and leucocytes, Grade 0 to 3. Quantitative estimation of urinary protein showed the presence of 0.2 to 0.8 Gm. in 100 cubic centimeters. In a single culture of urine, colon bacilli were present. Renal function was adequate as indicated by a standard urea clearance of 38 c.c., by a concentration of urea in 100 c.c. of blood of 28 mg., and by a urogram which revealed an early and considerable concentration of iodine compound in the renal calices and pelves. Blood studies indicated that results of the Kline flocculation test for syphilis were negative and secondary anemia was present. The hemoglobin concentration was 10.2 Gm. in 100 c.c., and the erythrocytes numbered 3,200,000 per cubic millimeter. The content of protein and albumin in the serum were definitely decreased and the lipid concentration in the plasma increased (Table IV). The electrocardiogram taken on February 28 was considered to be essentially normal (Fig. 11). A provisional diagnosis of subacute glomerulonephritis with nephrotic features was made. The history and some minor alterations in the calices of both kidneys as seen in urograms suggested mild chronic bilateral pyelonephritis.

The course of the patient's illness while she was in the hospital, from February 23 to March 21, was quite satisfactory. The edema responded to certain diuretic procedures, including diet, potassium nitrate, and three transfusions of blood (1,500 c.c. in all). The daily volume of urine varied from 700 to 2,400 cubic centimeters. The patient lost 18 pounds (8.2 kg.), and edema disappeared. The hemoglobin in the blood rose to normal and there was an increase in the serum protein and albumin. Arthritic manifestations were minimal, and her temperature was usually about normal though on a single occasion it rose to 100.6° F. A satisfactory explanation of the rheumatic complaints and manifestations of arthritis which she had on admission could not be made. On March 20 the urea clearance was 37 cubic centimeters.

After returning home on March 21 the patient felt much stronger and in the next three weeks gradually resumed her household duties. However, on April 6 the temperature rose to 102.5° F. and the following day the joints of her fingers and wrist began to swell. Later the periodic diarrhea and pain in the left anterior portion of the thorax recurred.

The second admission was on April 18, 1944. On examination the patient's temperature was 102° F., there was a butterfly papulocrythematosus rash on her face, and the joints of her fingers were swollen. The heart rate was 100 beats per minute and no murmurs or rubs were heard. Edema, Grade 2, was present in the legs. The blood pressure was 115/70 and on ophthalmoscopic examination the fundi were essentially normal, although the retinal arterioles and veins seemed distinctly dilated. A roentgenogram of the thorax revealed a possible mitral configuration of the heart. Several routine urinalyses revealed findings similar to those on her first admission; the quantitative estimate of protein in the urine was 0.1 to 0.5 Gm. in 100 cubic centimeters. Constituents of the blood were: hemoglobin, 10 Gm.; erythro-



Fig. 10.—(Case 2.) *a*, Glomeruli are destroyed and replaced by connective tissue (hematoxylin and eosin, $\times 150$). *b*, Dilated tubules filled with colloid casts (so-called colloid casts). Marked thickening of walls of arteries (hematoxylin and eosin, $\times 110$). *c*, Purulent exudate in tubules and small abscess may be noted to right (hematoxylin and eosin, $\times 90$).

cytes, 3,740,000; leucocytes, 5,200 to 13,400; urea, 56 mg.; serum sulfate, 10.8 mg.; serum protein, 4.2 Gm.; and the total lipoids of the plasma from 823 to 1,005 milligrams. The results of the Kline, Kahn, Hinton, and Kolmer tests of the blood serum for syphilis were negative.

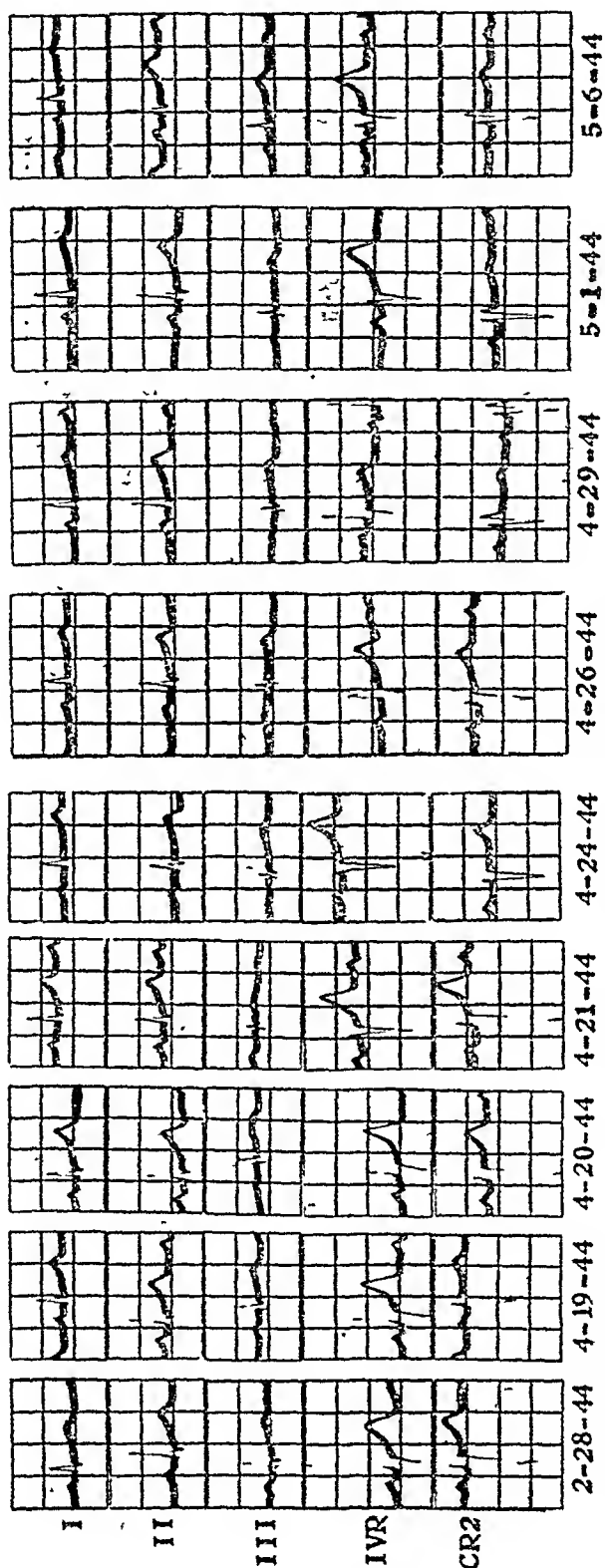


Fig. 11.—(Case 3.) Only by comparison of serial tracings is it possible to define changes suggestive of pericarditis. High-peaked T waves in Lead I are present in tracings taken on April 20 and 21 when a pericardial friction rub was first audible. The appearance of slight elevation of the RS-T segment in Lead III in the electrocardiogram of April 29 coincided closely with reappearance of the friction rub.

The patient was evidently still suffering from chronic glomerulonephritis in a nephrotic phase, but, in addition, evidences of toxemia including fever and an erythematous lesion in the skin of the face had developed.

TABLE IV. DATA ON BLOOD IN CASE 3

DATE (1944)	WHOLE BLOOD			BLOOD SERUM					BLOOD PLASMA			ELECTRO- CARDIOGRAM
	HEMO- GLOBIN (GM. IN 100 C.C.)	UREA (MG. IN 100 C.C.)	CREAT- ININE (MG. IN 100 C.C.)	NON- PROTEIN NITROGEN (MG. IN 100 C.C.)	PROTEIN (GM. IN 100 C.C.)	ALBUMIN (GM. IN 100 C.C.)	ALBUMIN- GLOBULIN RATIO	POTAS- SIUM (MG. IN 100 C.C.)	SULFATE (MG. IN 100 C.C.)	CHLORIDE (MG. IN 100 C.C.)	CARBON DIOXIDE COMBINING POWER (VOLUMES IN 100 C.C.)	
2/23	10.2	28		28	4.6							
2/24												
2/25*		20		34	3.9	2.0	1.1/1.0	15.6	5.2	660	50	ECG
2/28												
3/1†												
3/9		96	1.2	89	5.7	2.8	1.0/1.2	20.9	12.3			
3/15†		60	1.2					21.4	7.9			
3/18	13.3											
3/20		42										
4/18§	10.0	56		55	4.2	2.0	1.0/1.1		7.1			ECG 4-19
4/20								23.3	10.8	574		ECG 4-20, 21
4/22¶												ECG
4/28	90	90	1.5									ECG 4-24, 26
5/5	144	144	2.5	105	3.3	1.4	1.0/1.3					ECG 4-29, 5-1
5/6	130											ECG
5/15	164		2.1					22.2	11.4	583		
5/22												ECG
												Patient died

*Plasma cholesterol, 327 mg. in 100 cubic centimeters.

†Serum calcium, 7.9 mg.; serum phosphorus, 4.1 mg. in 100 cubic centimeters.

‡Plasma cholesterol, 240 mg.; cholesterol esters, 203 mg.; lecithin, 405 mg.; total fatty acid, 747 mg.; total lipoids, 937 mg. in 100 cubic centimeters.

§Plasma cholesterol, 277 mg.; total fatty acid, 546 mg.; total lipoids, 823 mg. in 100 cubic centimeters.

||Plasma cholesterol, 293 mg.; cholesterol esters, 182 mg.; lecithin, 458 mg.; total fatty acid, 712 mg.; total lipoids, 1,005 mg. in 100 cubic centimeters.

¶Vitamin C content of plasma, 0.5 mg. in 100 cubic centimeters.

electrocardiogram taken on this day the elevation of the RS-T in Lead III was somewhat more definite than that in the tracing made on April 26 (Fig. 11). During the remaining twenty-three days of the life of the patient a friction rub was heard over the heart intermittently. In the final tracing taken on May 6 (Fig. 11), no definite signs indicative of pericarditis were present.

On April 24 to 26 a loud blowing systolic murmur was heard over the apical region of the heart. Three attempts to grow an organism from the blood were unsuccessful. Uremia gradually developed, and on May 5 the concentration of urea in the blood had increased to 144 milligrams. The blood creatinine was elevated to 2.5 mg. on the same day, and on May 6 the serum sulfate increased to 11.4 milligrams. Because the patient had intermittent attacks of diarrhea, a roentgenogram of the colon was taken following a barium enema on May 9. Ulcerative colitis was found. Stomatitis was demonstrable on May 14 and signs of pneumonia were present in the lower lobe of the left lung the next morning. Up to this time the daily volume of urine during this stay in the hospital varied from 800 to 1,500 cubic centimeters. From May 14 until her death, eight days later, the patient lapsed periodically into semicomatose, found it difficult to swallow food or fluids, and passed urine involuntarily. She died at 6:40 A.M., May 22.



Fig. 13.—(Case 3.) Subacute glomerulonephritis.

Differences of opinion were often expressed as to the clinical diagnosis of this patient's condition while she was under observation in the hospital. However, shortly before her death we were convinced that she was suffering from a general diffuse disease and that the skin lesion, colitis, diffuse nephritis, endocarditis and pericarditis were manifestations of the disorder which Libman and Sacks¹⁰ first described in 1923 and since has been termed by many as the "Libman-Sacks syndrome."¹¹

Necropsy.—There was moderate pretibial edema. The peritoneal cavity contained 500 c.c. of cloudy, opalescent fluid. There were fibrinous adhesions from the omentum to the bladder, descending colon, uterus, and anteriorly to the abdominal wall. The right pleural cavity contained 750 c.c. of fluid and flecks of fibrin. There were fibrinous adhesions between the pericardium and lung. The left pleural cavity contained 1,500 c.c. of dark amber fluid. The pericardial sac measured 16 cm. in transverse diameter and contained 250 c.c. of sanguino-

On April 19 a soft systolic murmur could be heard over the mitral region of the heart. The patient complained of pain in the left side of the thorax and dyspnea. During the afternoon of April 20 her temperature rose to 102.6° F., and a definite precordial friction rub developed and persisted for forty-eight hours. Electrocardiograms taken on April 19, April 20, and April 21 were not strikingly different from the initial electrocardiogram recorded two months earlier, on February 28. There was an increase in the height of the T wave in Leads I,

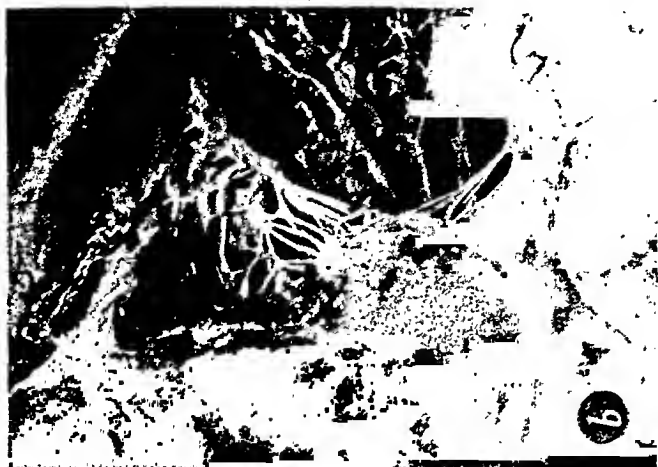


Fig. 12.—(Case 3.) *a*, Fibrinous pericarditis. *b*, Vegetative mitral endocarditis (nonbacterial).

II, and IVR and the apex of the deflection was sharper (Fig. 11). From April 23 to 27, inclusive, no friction rub was heard and the temperature did not rise above 99° F. In the electrocardiogram recorded on April 26, a slight change or elevation in the configuration of the RS-T segment in Lead III could be defined (Fig. 11). On April 28 and 29, a loud friction rub was audible. On April 29 the patient's temperature rose to 101.7° F. In the

The pleura of the lungs contained many petechiae. There was granular fibrinous exudate on the pleural surface of the right lower lobe. Firm, nodular consolidated areas could be felt in both lower lobes. The left lung was almost completely collapsed.

The right kidney weighed 170 grams and the left weighed 194 grams. Aside from a slightly granular surface and a few small petechiae, the kidneys were not remarkable grossly (Fig. 13). The brain appeared grossly normal except for a few small petechiae in the left basal nuclei.



Fig. 15.—(Case 3.) *a*, Myocarditis. Focal collection of polymorphonuclear cells and necrosis of muscle fibers can be noted (hematoxylin and eosin, $\times 145$). *b*, Mitral endocarditis. Fibrinoid degeneration of connective tissue, necrosis, and purulent exudate (hematoxylin and eosin, $\times 135$).

Histologic Examination.—There was a thick fibrinous exudate over the pericardial surfaces. Organization of this exudate by masses of fibroblasts was taking place (Fig. 14, *a*). Although most of the fibrinous exudate was acidophilic, there were many masses and threads of fibrin which took the hematoxylin stain. Sections of the left ventricle and auricle revealed

fibrinous exudate. Fibrinous exudate covered the visceral and parietal layers of the pericardium (Fig. 12; a).

The heart weighed 336 grams (normal, 230 grams). The mitral valve was thickened and edematous. There was a row of granular, pyramidal-shaped vegetations along the line of closure of most of the posterior mitral leaflet and a similar but shorter row on the



Fig. 14.—(Case 3.) a, Pericarditis. Organization of the fibrinous exudate by fibroblasts can be seen (hematoxylin and eosin, $\times 130$). b, Mural endocarditis. Edema and fibrinopurulent exudate are shown (hematoxylin and eosin, $\times 135$).

anterior leaflet (Fig. 12, b). Some of these vegetations extended over the surface of the leaflet and up on the auricular wall. Similar granular but flatter vegetations were also found on the chordae tendineae. On the endocardial surface of the left ventricle, 2 cm. below the aortic valve, there was a flat granular mural vegetation. There were a few small vegetations on both surfaces on the tricuspid leaflet.

had produced very cellular glomerular tufts and occlusion of the capillaries. Fusion and necrosis of these endothelial cells and various portions of the tufts had occurred. Adhesions of the tuft to the capsule were observed frequently. Hyaline thickening of the basement membrane of the capillaries (wire looping) and fibrous crescents were occasionally found. The tubules generally appeared normal. Frozen sections stained for fat revealed a mild degree of infiltration of fat into some of the epithelial cells of the convoluted tubules. A few tubules contained red blood cells and a few contained albuminous material. The arteries and veins appeared normal (Fig. 16, *a* and *b*).

Section of the lung revealed a fibrinopurulent pleuritis, purulent bronchitis, and lobular pneumonia. In sections of the right main stem bronchus there was a bandlike area of fibrinoid degeneration and necrosis immediately beneath the epithelium.

There was severe edema of the submucosa of the colon.

The following diagnoses were made: (1) vegetative mitral, tricuspid, and mural endocarditis; (2) fibrinous pericarditis, pleuritis, and peritonitis; (3) subacute glomerulonephritis; (4) bronchopneumonia; (5) focal myocarditis; (6) edema of mucosa of colon; (7) hypertrophy of heart; and (8) petechiae of left basal nuclei of brain.

OBSERVATIONS

Clinical Observations.—It was possible in three cases, by clinical observation, to recognize the early development of acute pericarditis and follow its subsequent course. The initial rub over the precordium was first audible thirty days, seven days, and thirty-three days before death in Cases 1, 2, and 3, respectively. This period of one to four and one-half weeks provided an unusual opportunity to study pericarditis during its entire course. Observations, including electrocardiograms, which could be used as controls were made in two cases during a previous visit of the patients to the clinic and in all three cases at the time of last admission to the hospital. In Case 2, in which the patient made only one visit to the clinic, clinical, chemical, and electrocardiographic observations extended over a period of forty days before the onset of pericarditis.

Cases 1 and 2 presented the clinical features so often seen in terminal chronic uremia. Perhaps the most striking objective development in these two cases was that of a diffuse membranous stomatitis, so-called uremic frost. It occurred in each instance at approximately the time of onset of the pericarditis. The toxemia due to uremia was severe, as indicated by convulsive seizures and mental disturbances. A noticeable increase in temperature occurred with the onset of pericarditis. It is of some interest that in Case 1 after the initial development of pericarditis there followed an interim period of fourteen days during which the temperature fell to the normal level and the pericardial rub was no longer audible. Subsequently, a rise in temperature accompanied the recurrence of the rub. In contrast, in Case 2 the signs of pericarditis persisted from onset throughout the course. In the experience of most observers this is the usual course of events in similar cases. In Case 3 the primary cause of renal, pericardial, and other pathologic lesions is the little-understood etiological factor in the Libman-Sacks syndrome.^{10, 11} Therefore, toxemia of uremia was probably a secondary and minor causative factor.¹² In this case the pericardial rub and increase of body temperature occurred almost simultaneously. These

a fibrinopurulent exudate on the endocardial surface (Fig. 14, *b*). In the myocardium there were hyaline thrombi in small vessels and focal and interstitial collections of polymorphonuclear cells with necrosis of some muscle fibers (Fig. 15, *a*). In sections of the mitral valve the vegetations were found to consist largely of fibrinopurulent exudate (Fig. 15, *b*).

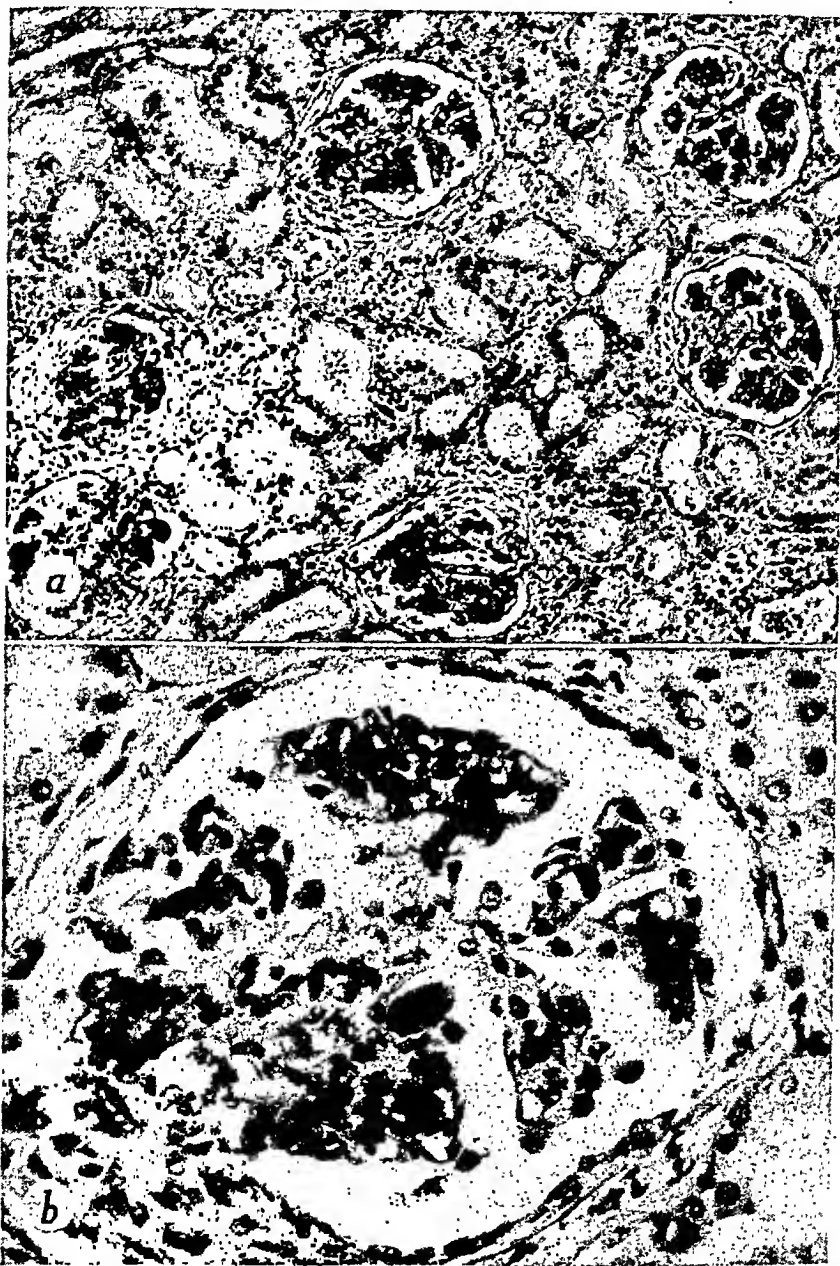


Fig. 16.—(Case 3.) *a* and *b*, Subacute glomerulonephritis. Proliferation of endothelial cells, fusion, and focal necrosis (*a*, hematoxylin and eosin, $\times 90$; *b*, $\times 325$).

There were patches of fibrinoid degeneration of the connective tissue of the leaflet with actual necrosis in some places. Large numbers of polymorphonuclear cells were present in these areas. In addition to these foci there was an acute diffuse inflammation of the entire leaflet. The latter was well vascularized by capillaries as well as by arteries and veins. The tricuspid valve was the seat of a similar but less extensive inflammatory process.

In sections of the kidney no normal glomeruli could be found. The most pronounced change was an extensive increase in the number of endothelial cells in the capillaries. This

are not exceptionally great. However, in Cases 1 and 2, the changes were of sufficient extent to be definitive,¹³ and in all three cases, such alterations as did occur were coincidental with the other manifestations of the pericarditis. In Case 2, slight changes appeared in the electrocardiogram five days before a friction rub was audible. In Case 1 no definite electrocardiographic changes were recorded until five days after a friction rub was first heard. In general, however, the period of maximal intensity of the friction rub coincided with the occurrence of maximal electrocardiographic changes of the type associated with pericarditis. It is of interest that in Cases 1 and 3 both the friction rub and the electrocardiographic changes disappeared only to reappear at a later time (Table V).

TABLE V. RELATION OF AUDIBLE PERICARDIAL RUB AND BODY TEMPERATURE TO ELECTROCARDIOGRAPHIC DATA

CASE	DATE	PERICARDIAL RUB*	BODY TEMPERATURE, DAILY MAXIMUM (°F.)	ELECTROCARDIOGRAM†	
				RS-T SEGMENT ALTERATIONS	T-WAVE ALTERATIONS
1	1943				
	6/11	Inaudible	99	0	0
	6/16	Distinct‡	98.6		
	6/17	Inaudible	100	0	0
	6/21	Loud	100.2	+	+
	6/23	Loud	99.4	+	+
	6/24	Loud (4)	99.4		
	6/25	Inaudible	98.6	+	+
	6/28	Inaudible	98.6	±	±
	7/ 2	Inaudible	98.6	±	±
	7/ 7	Inaudible (13)	100		
	7/ 8	Loud	99	+	+
	7/14	Loud (7)	100.2	+	+
2	1944				
	2/11	Inaudible	97.4	0	0
	2/16	Inaudible	99.4	+	+
	2/20	Inaudible (10)	100.6		
	2/21	Loud	100.6	+	+
	2/23	Loud	100	+	+
	2/25	Loud	99	+	+
	2/26	Loud	98.4	+	+
	2/27	Loud (7)	98		
3	2/28	Inaudible	97	0	0
	4/19	Inaudible	103.4	0	+
	4/20	Loud	102.6	0	+
	4/21	Loud	99.4	0	+
	4/22	Loud (3)	98.7		
	4/24	Inaudible	98.6	0	+
	4/26	Inaudible	98.6	+	+
	4/27	Inaudible (5)	99		
	4/28	Loud	99.6		
	4/29	Loud (2)	101.7	+	
	5/ 1	Inaudible	98.8		
	5/ 3	Inaudible (3)	100.4		
	5/ 6	Loud (3)	102	0	0
	5/ 8	Inaudible (2)	100.4		

*The numbers in parentheses indicate the number of consecutive days in which the condition was present.

†0 = No distinctive alterations. + = Elevation of RS-T segment or T wave. ± = Isoelectric RS-T segment or isoelectric or diphasic T wave.

‡Distinct but not loud rub.

were intermittent as in Case 1. The increase in temperature, however, was more definite than in Cases 1 and 2. The course of the pericarditis in Case 3 was the longest. The development of stomatitis and mild colitis during the course of the pericarditis is of interest.

Chemical Studies of Blood and Urine.—The greatest alterations in the blood and urine occurred in Case 1. The concentrations of urea, creatinine, sulfate, and phosphorus in the blood were extremely high throughout the last illness (Table I). The lipid content of the plasma was also increased. The concentration of potassium in the serum varied from an abnormally low content to a slight increase above the normal. The decrease in concentration of hemoglobin, chloride, sodium, and calcium in whole blood, plasma, and serum was also typical of severe uremia. Hypoproteinemia was moderate in degree and there was slight, if any, tendency to acidosis, the carbon dioxide combining power varying from 62 to 38 volumes in 100 cubic centimeters. The balance of total basic to acid ions is distinctly on the basic side (Table II). The excretion of protein in the urine was considerable, amounting to about 1 to 2 Gm. in 100 cubic centimeters.

In Case 2 also the chemical evidence of uremia was definite. However, the urea, creatinine, sulfate, and phosphorus indicated less renal insufficiency than in same period of illness in Case 1. The rise in potassium was somewhat greater than in Case 1. There was only a slight increase in plasma lipids. The hypoproteinemia was moderate in degree. In addition to the anticipated decrease in concentration of hemoglobin, chlorides, and sodium, definite acidosis was present as demonstrated by the carbon dioxide combining power of the plasma of 24 volumes in 100 c.c. on the day of death. This finding differs from that in Case 1 in which there was little or no acidosis. The protein content of the urine (0.3 Gm. in 100 c.c.) was also distinctly less than in Case 1.

The alterations in the blood in Case 3 reveal a distinctly milder degree of uremia than in the other two cases.¹² Urea, creatinine, and sulfate rose only to 164, 2.5, and 11.4 mg., respectively. The potassium concentration fluctuated at the upper limit of normal. There was a definite increase, greater than in Cases 1 and 2, in all the lipid fractions of the plasma. The reduction in the content of serum protein and albumin was considerable. These alterations in protein and lipid content were in harmony with the distinct tendency to nephrosis in this patient. The terminal reduction in the hemoglobin in Case 3 was distinctly less than in the other two cases. This finding, together with the observation that the hemoglobin increased rapidly after transfusions during the patient's first visit, indicates a much less toxic condition of the bone marrow than is usually the case in chronic, severe uremia (Cases 1 and 2). The concentration of protein in the urine at the time of the patient's first admission was considerable, varying from 0.2 to 0.8 Gm. in 100 cubic centimeters. There was additional evidence as late as one month before the onset of pericarditis that renal function was not as severely impaired as in Cases 1 and 2; for at that time the standard urea clearance was 37 c.c., an approximately normal value.

Electrocardiographic Observations.—The degree of RS-T segment elevation and the changes in T-wave configuration in the electrocardiograms reproduced

by Chauffard and Huber,¹⁹ Marantis,²⁰ Leplat,²¹ and Barach.²² The present study goes further in revealing both clinical and electrocardiographic evidence that pericarditis can occur, subside, and recur in the same uremic patient. The pathologic lesions found at necropsy in Case 1, after pericarditis had been present intermittently for one month, were compatible with an intermittent course.

The comparatively slight changes in the electrocardiogram throughout the course of the pericarditis in Case 3 indicate that persistent fibrinous pericarditis of considerable degree can take place with minimal electrocardiographic alterations. This suggests the possibility that demonstrable electrocardiographic changes may be entirely absent in acute pericarditis. Such a suggestion is consistent with the observations of previous investigators.²³ This study of three cases emphasizes that during the course of uremic pericarditis only minimal disturbances may occur in the distribution of the electrical potentials developed in the heart.

The variability among cases in the degree of electrocardiographic changes occurring during episodes of pericarditis is not readily explained. Since only small amounts of fluid were found in the pericardial sac in all three cases, the presence or absence of electrocardiographic changes can not be ascribed to cardiac tamponade, nor is the variability in electrocardiographic changes to be accounted for solely on the basis of existence of myocarditis.²³ In only one of the three cases (Case 3) was there histologic evidence of myocarditis, and it was in this case that electrocardiographic indications of pericarditis were appreciable only on closest scrutiny of serial tracings. Electrocardiograms were taken at relatively short intervals before, during, and after the friction rub could be heard. When electrocardiographic alterations occurred, they evolved slowly. Hence, it is unlikely that significant changes in the distribution of electrical potentials existed for some brief interval but were not recorded.

Just why in some cases the potentials which develop after cellular injury are productive of significant electrocardiographic changes, whereas in other cases they are not, remains an unanswered question. Perhaps, the solution should be sought in a study of the speed with which the pericarditis and the attendant cellular injury progress and regress. But that a complete answer would be obtained by such a study appears doubtful.

The actual cause of pericarditis in uremia is not understood. Several possible factors can be eliminated in our cases. Syphilis and tuberculosis were absent. There were no evidences of septicemia in Cases 1 and 3. The pathologic and bacteriologic studies of Barach²² show that uremic pericarditis may have an infectious origin in some cases while in others no bacteria or tissue reactions of infection are present. The histologic lesion in Case 2 is suggestive of an infectious process, but similar changes were absent in Cases 1 and 3. What then can be the toxic etiological factor? This question was raised by Duhot and Hallez in 1913.²⁴ The presence of a definite acidosis in the blood in certain of his cases led Barach to consider acidosis as a possible toxic factor. But the findings of several subsequent investigators indicate that grave uremia can be

Pathologic Observations.—The gross appearance of the pericardial inflammation varied greatly.^{14, 15} In Case 1 the exudate was predominantly hemorrhagic; in Case 2 it was purulent; and in the third case it was fibrinous. The histologic study of the inflammatory process did not answer the question of what etiological factors were concerned. The exudate in Case 1 was more hemorrhagic than is usually observed in so-called uremic or "chemical" pericarditis, but no apparent reason for this could be demonstrated histologically. In Case 2 the purulent character of the exudate coincided with the finding of colonies of bacteria which were gram-positive cocci. The exact nature of the organisms could not be determined because cultures were not obtained. The possibility that they were post-mortem invaders must be considered. No organisms could be demonstrated in Case 3. In all three cases the well-developed organization of the pericardial exudate indicated that the inflammatory process had been present for some time. In Case 1, in addition to the exudative lesion, there were organizing fibrinous adhesions which suggested a healing process. These findings support the clinical observations of initial pericarditis, remission, and later recurrence. Myocardial lesions were found only in Case 3.

The renal lesions deserve comment. In Case 1 there was typical glomerulonephritis. The fact that lesions identical with those described as Kimmelstiel-Wilson's disease⁹ were also present emphasizes the nonspecific character of so-called intercapillary glomerulosclerosis. Identical lesions have also been observed by others in cases of hypertension and cases of glomerulonephritis without diabetes.¹⁶ The fact that no normal glomeruli could be found gives histologic support to the clinical diagnosis of renal insufficiency. The renal lesions in Case 2 were largely those of active and healed pyelonephritis. The possibility that chronic glomerulonephritis also was present cannot be entirely dismissed since few normal glomeruli could be found. Nevertheless, it is well known that glomerular destruction also occurs extensively in pyelonephritis. The renal lesions in Case 3 represented a more recent inflammatory process than was present in Cases 1 and 2. The lesions were much more extensive than those usually observed in lupus erythematosus or Libman-Sacks disease. The diffuse proliferation of the endothelium of the glomerular capillaries, the focal necrosis of portions of the glomerular tuft, and the occasional occurrence of hyaline thrombi in the glomerular capillaries and afferent arterioles resembled strongly the type of lesion found in subacute bacterial endocarditis. Nevertheless, similar lesions have been observed in cases of lupus erythematosus in the absence of endocarditis¹⁷ and in uncomplicated glomerulonephritis. The histologic features of the cardiac lesions of this case and the persistently negative blood cultures were consistent with a diagnosis of lupus erythematosus or Libman-Sacks disease.

COMMENT

✓ The occurrence of pericarditis in chronic uremia has in the past been considered a final incident in the course of the disease.¹⁸ There is evidence, however, that, even in the late stages of chronic uremia, pericarditis may develop and run its course and healing may take place. Such cases have been reported

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METHODS OF CHEMICAL ANALYSIS EMPLOYED IN THE PRESENT STUDY

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- Creatinine.—Folin, O. K.: Laboratory Manual of Biological Chemistry; With Supplement, ed. 3, New York, 1922, D. Appleton-Century Company. pp. 149, 245, and 247.

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Serum

- Total proteins.—Macro-Kjeldahl technique of estimation of total nitrogen and total protein calculated after subtracting nonprotein nitrogen as estimated by the micro-Kjeldahl method.
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present in the absence of severe acidosis.²⁵ This fact receives added confirmation in the data recorded in Case 1. Other significant alterations of the inorganic ions in the blood occur in uremia. These include a decrease in concentration of chloride, sodium, and calcium and increase in the concentration of phosphate, sulfate, and potassium. In our cases none of these changes, single or combined, appear to have definite significance as a cause of the pericarditis. The actual concentration of serum potassium in this series is interesting. Only in Case 2 did the serum potassium increase appreciably. The highest level was 25.6 mg. in 100 c.c., and this concentration does not usually lead to alterations in electrocardiographic tracings such as occur in pericarditis. It is interesting that when both potassium intoxication (serum potassium, 40 mg. in 100 c.c.) and pericarditis occurred in one of our patients in a former series of cases of uremia, the electrocardiogram revealed intraventricular block, but no RS-T segment changes typical of pericarditis.²⁶ Therefore, the concentration of potassium ions in the serum is not a decisive factor in the development of the electrocardiographic changes characteristic of pericarditis.

New microchemical methods have greatly increased knowledge of the many chemical alterations that can occur in chronic uremia, but to date no alteration in a single chemical constituent, nor a combination of changes in the blood has been found which invariably accompanies the clinical picture of uremia including pericarditis. All the known data support the conception of chemical uremia in which infection may play a secondary role.

CONCLUSIONS

Acute pericarditis occurs frequently in chronic uremia. Clinical, electrocardiographic, and pathologic studies indicate that uremic pericarditis is a process which undergoes exacerbations and remissions and may even heal. It is an incident in the course of advanced renal insufficiency, but not inevitably a terminal incident. Like so many of the complications of uremia, its actual etiology is still unknown. However, the greatly altered chemistry present in the uremic patient must be an important etiological factor.

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PAROXYSMAL VENTRICULAR TACHYCARDIA

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CLINICAL experience has led us to regard paroxysmal ventricular tachycardia as a very serious condition. This arrhythmia is usually associated with acute myocardial infarction or with digitalis intoxication and may be followed by ventricular fibrillation and death. However, a few instances of paroxysmal ventricular tachycardia have been reported in which there were no signs of organic heart disease.

The purpose of this communication is to report four unusual instances of ventricular tachycardia from which the patients recovered. In one instance, the tachycardia complicated myocardial infarction and persisted for twenty-six days. In another (Case 4), the electrocardiogram showed the rarely occurring condition of alternating direction of ventricular complexes during the paroxysmal tachycardia. In the other two (Cases 2 and 3), the attacks occurred in patients without organic heart disease.

CASE 1.—J. G., a 54-year-old farmer, gave a history of scarlet fever at the age of 14 years. There was no history of rheumatic fever. In January, 1941, he noticed a heavy pressure in the cardiac region, especially after meals. The pressure gradually became continuous, very severe, and was accompanied by pain radiating to both arms. He remained in bed for two months. He took 0.1 Gm. ($1\frac{1}{2}$ grains) of digitalis twice daily for eleven months. On Dec. 5, 1941, he suddenly felt a "flushing sensation" in the chest for which he was hospitalized. He had suffered no definite pain and only slight shortness of breath.

Examination revealed a strongly built man whose height was 5 feet 8 inches and whose weight was 178 pounds. There was slight pallor and slight engorgement of the cervical veins. The heart was not enlarged; the rhythm was regular, and the rate was 180 per minute. The sounds were of normal quality. The second aortic and pulmonic sounds were faint. The blood pressure was 90/70. The physical examination was otherwise negative.

The temperature, sedimentation rate, and white blood count were normal. The Kahn test was negative. Carotid sinus and ocular pressure had no influence on the cardiac rate. The electrocardiogram showed ventricular tachycardia (Fig. 1, a).

An intravenous injection of 10 c.c. of 25 per cent magnesium sulfate had no effect. Quinidine sulfate was then administered in doses of 6 grains every four hours, a total daily dose of 36 grains. Since this dosage proved ineffective, it was increased on the seventh day to 8 grains every four hours (total daily dose, 48 grains). This dosage also failed to control the attack (Fig. 1, b).

Digitalis was then given in doses of 3 grains twice daily, but was discontinued after three days because of nausea and vomiting. On the fifteenth day, quinine dihydrochloride in a dose of $7\frac{1}{2}$ grains was given intramuscularly and 8 grains of quinidine sulfate were administered orally every four hours. Both drugs were well tolerated by the patient, but the attack remained uncontrolled. During the following days the intramuscular injection of quinine

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Potassium.—Kramer, Benjamin, and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Potassium in Small Amounts of Serum, *J. Biol. Chem.* 46: 339, 1921.

This method in our hands has checked with gravimetric procedures. The precipitation by sodium cobaltinitrite was allowed to proceed for forty-five minutes at icebox temperature in order to obtain a good, granular precipitate. If this and other steps are rigorously adhered to, the method is satisfactory.

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Total nitrogen.—Kjeldahl, J.: Neue Methode zur Bestimmung des Stickstoffs in organischen Körpern, *Ztschr. f. anal. Chem. Wiesb.* 22: 366, 1883.

Urea.—Same method as for estimation in whole blood.

Total proteins.—Macro-Kjeldahl method for estimation of total nitrogen. Estimation of nonprotein nitrogen by macro-Kjeldahl method after precipitating the protein by Folin's tungstic acid reagent method. Total proteins calculated after subtracting the nonprotein nitrogen from the total nitrogen and multiplying by 6.25.

(0.14 second), a slightly depressed RS-T segment in Lead I, and elevated RS-T segments in Leads II and III (Fig. 1, c).

During the following three days the patient was given three grains of quinidine sulfate once daily. He felt well except for slight nausea and troublesome hiccups. The cardiac rate averaged 84 per minute. The blood pressure was 105/60. The temperature, sedimentation rate, and white blood count were normal. On the fourth day after the cessation of the attack the patient was seized at 8 A.M. with another attack of paroxysmal tachycardia. The electrocardiogram showed the same form of ventricular tachycardia as had been recorded previously.

The patient was immediately given 9 grains of quinidine sulfate orally. Two hours later he was given 12 grains orally. Since the tachycardia was unaffected, an oral dose of 12 grains was repeated two hours later and at the same time an intramuscular injection of $7\frac{1}{2}$ grains of quinine dihydrochloride was given. The patient felt slightly nauseated; two hours after the last administration normal rhythm reappeared. The heart rate was 90 per minute, the blood pressure was 100/60, and the electrocardiogram was similar to that taken after the first attack.

On the following days the patient felt well. The blood pressure gradually rose to 125/90. The electrocardiogram remained unchanged, except for the T wave in Lead I, which became distinctly negative (Fig. 1, d). The patient received six grains of quinidine sulfate once daily until he was discharged sixteen days after the second attack.

Subsequent Course.—The tachycardia did not reappear. The electrocardiogram showed the pattern of posterior wall myocardial infarction (Fig. 1, e). The patient felt well during the following three years, until October, 1944, when he suffered an attack of myocardial infarction. The electrocardiogram showed small, notched QRS complexes in all three leads and a small R wave in the chest leads (Fig. 1, f). He responded well to treatment and has no discomfort at present.

CASE 2.—L. D., a 39-year-old laborer, gave a history of pneumonia in childhood, an appendectomy at the age of 23, and gonorrhea at the age of 29 years. There was no history of rheumatic fever. He smoked ten cigarettes daily and took no alcohol.

In 1937, when he was 35 years of age, he experienced a sudden attack of palpitation while working. The attack lasted a few minutes and disappeared suddenly. From that time on the attacks occurred almost every week and lasted for two or three days. After the attack subsided the patient felt well and was able to resume his work.

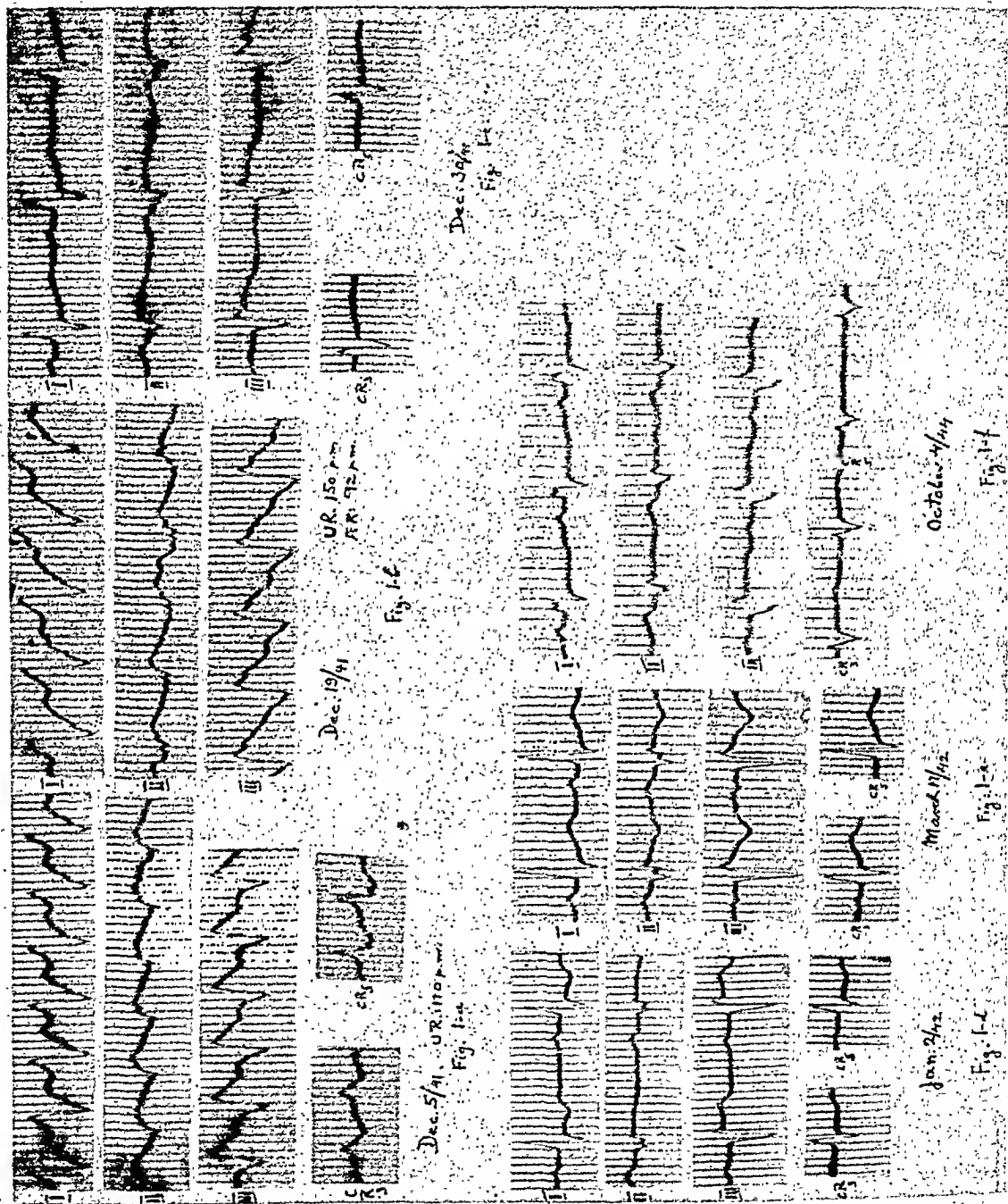
On May 15, 1941, the heart was normal in size, the rhythm was regular, and the rate was 240 per minute. The heart sounds were normal, and the blood pressure was 100/60. The remainder of the examination was negative. The sedimentation rate and white blood count were normal. The Kahn test was negative. The electrocardiogram showed ventricular tachycardia with a ventricular rate of 240 per minute (Fig. 2, a). The P waves were clearly visible. The auricular rate was 100 per minute. Carotid sinus and ocular pressure had no influence on the cardiac rate.

The patient was given 6 grains of quinidine sulfate every three hours; after the third dose the attack subsided. The electrocardiogram showed regular sinus rhythm, a normal P-R interval, and a normal QRS complex. The T waves were of low amplitude and slightly inverted in Lead I, and of increased amplitude in Leads II and III. In the chest leads the R wave was absent and the T wave was inverted (Fig. 2, b). Nine days later the standard leads were normal but the R wave was still small in the chest leads. After two more days the electrocardiogram was normal (Fig. 2, c and d).

A single dose of six grains of quinidine sulfate was given daily for the following two weeks. Since the patient remained free of attacks he was discharged from the hospital at the end of this period. When he was seen two months later he stated that he felt well and had gained weight, but that he experienced frequent short attacks of tachycardia if quinidine was discontinued. A single dose of less than 9 grains had no effect on these attacks.

CASE 3.—J. E. A., 38, a housewife, was first seen on Sept. 3, 1942. She gave no history of rheumatic fever or of infectious diseases. After the birth of her second child, in

dihydrochloride ($7\frac{1}{2}$ grains) was continued, and the oral dose of quinidine sulfate was increased to 8 grains every three hours. On the twentieth day the dose of quinidine sulfate was increased to 15 grains every three hours, but the attack persisted.



On the twenty-sixth day, in view of the continuous tachycardia, 30 grains of quinidine sulfate were given in a single dose at 10 A.M. Two hours later, since the rhythm was unaffected, another dose of 30 grains was given. One hour later the patient developed an ashen pallor, perspired profusely, became nauseated, and vomited a large amount of undigested food. At 5 P.M. a sudden change in rhythm occurred. The cardiac action became regular with a rate of 80 beats per minute. The blood pressure was 85/55. The electrocardiogram showed regular sinus rhythm, a normal P-R interval, notched and widened QRS complex

blood count, and sedimentation rate were normal. The Kahn test was negative. The electrocardiogram was normal (Fig. 3, a).

On the following day, after a short walk, the patient noticed frequent irregular beats. An electrocardiogram showed coupled and quadrupled ventricular extrasystoles (Fig. 3, b).

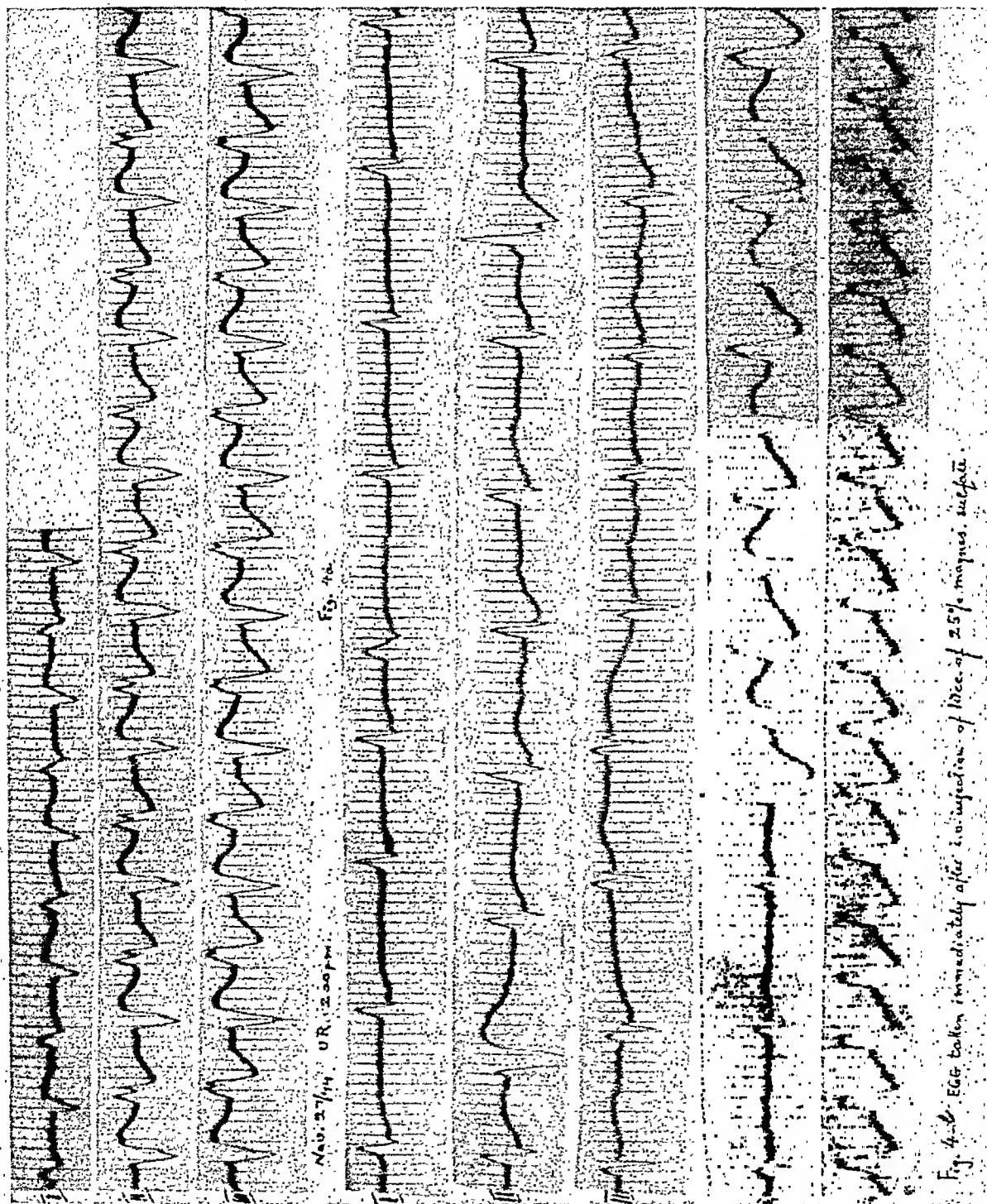


Fig. 4. ECG taken immediately after intravenous injection of 25% magnesium sulfate.

FIG. 4.

During the electrocardiographic registration she was seized with a sudden attack of ventricular tachycardia which lasted about ten minutes (Fig. 3, e). Carotid sinus and ocular pressure did not affect the paroxysm. The attack subsided suddenly. An electrocardiogram made after the attack showed a low T wave in Lead II, and a slight inversion of the T wave in Lead III which became more distinct on the following day (Fig. 3, d).

During the following ten days, during which she was hospitalized, the patient was given estradiol intramuscularly and 3 grains of quinidine sulfate four times daily. She ex-

in the chest leads disappeared. Thus the pattern of the electrocardiogram became similar to that of anterior myocardial infarction (Fig. 2, b).

The occurrence of inverted T waves following an attack of paroxysmal tachycardia has been previously described, but opinion as to the interpretation of this phenomenon is still not uniform. In Cases 2 and 3 the inverted T waves disappeared after ten days and three weeks, respectively, and the electrocardiograms became normal. The short duration of the abnormal electrocardiograms suggests that they are due to myocardial ischemia caused by the paroxysmal attack. The absence of the R wave in the chest leads indicates that the ischemia affected the anterior wall.

The ventricular tachycardia with alternating form of the ventricular complexes, noted in Case 4, usually occurs in patients who have severe myocardial damage and are under digitalis therapy.^{1, 2, 19, 20, 22, 23} It is generally considered a fatal condition; in fact, in all the reported cases except one,²³ death has occurred either during the attack or within a short period thereafter.

Various explanations of the mechanism of the alternating form of paroxysmal ventricular tachycardia have been offered. One theory is that two independent foci, one in each ventricle, alternately initiate the contractions. According to another theory, the cardiac impulse arises in a single focus situated at the bifurcation of the bundle of His and, due to a defect in the bundle branches, the impulse is transmitted alternately over the right and left branches, thereby producing the picture of bundle branch block.^{2, 19, 20} The possibility of a double ventricular circus movement has also been suggested.²¹

The absolute regularity of the rhythm in these tachycardias leads us to favor the theory of a single focus, since the assumption that two independent foci are present would make it difficult to explain the regular rhythm.²⁰ Scherf and Kisch,²² in a careful analysis of their cases, have been able to demonstrate that the stimuli originate in one center and that the change in the form of the ventricular complexes is due to disturbance of the intraventricular conduction. The regular rhythm in the paroxysmal tachycardia supports the view of a single focus with impairment of the bundle branch conduction.

TREATMENT

Although the value of quinidine sulfate in the treatment of attacks of paroxysmal tachycardia is generally recognized, there is still some difference of opinion with regard to its usefulness, the dosage, and the mode of administration.^{6, 8, 18} The usual dose varies between 5 and 15 grains, given orally at intervals of two or three hours. Rarely is a single dose exceeding 20 grains recommended, although a single dose of 40 grains has been reported.¹⁹ If oral administration remains ineffective, intramuscular or intravenous injection of quinidine dihydrochloride is recommended. Intramuscular injection of quinidine dihydrochloride was without effect in Case 1. However, Riseman and Linenthal¹¹ report that it is helpful in cases in which vomiting or poor absorption from the gastrointestinal tract is present.

In view of the extreme danger and risk attending the intravenous injection of quinine, it is advisable to abandon this method of administration. In

perienced no attacks and had no complaints even after an hour's walk. When the patient was seen two weeks later, after discharge from the hospital, she stated that the irregular beats still occurred for short periods and were followed by attacks of rapid palpitation.

During this period she had been taking 3 grains of quinidine sulfate twice daily. This was increased to 9 grains taken as a single daily dose. When seen six weeks later the patient stated that the dose of 9 grains was well tolerated and that she had experienced no further irregular beats.

CASE 4.—The patient, a 57-year-old man, suffered from cardiac failure due to hypertensive heart disease. Cheyne-Stokes breathing, hydrothorax, edema, and auricular fibrillation were present. He was extremely sensitive to digitalis. Even a single dose of $1\frac{1}{2}$ grains caused nausea and vomiting. When he was given $1\frac{1}{2}$ grains twice daily, he developed a sudden attack of tachycardia which the electrocardiogram showed to be of ventricular origin and which was characterized by alternating direction of the ventricular complexes (Fig. 4, a). Intravenous injection of 10 c.c. of 25 per cent magnesium sulfate stopped the attack. However, after approximately three minutes the tachycardia reappeared. For a brief period the ventricular complexes were bidirectional. Soon, however, the ventricular beats became unidirectional (Fig. 4, b). Digitalis was discontinued and 9 grains of quinidine were given orally. The attack stopped after two hours. During the following seven days, 3 grains of quinidine were given once daily. The attack did not reappear. The patient improved gradually, and when last observed, six months after the original seizure, was in fairly good condition.

DISCUSSION

The striking feature of the clinical picture in Case 1 was the complete absence of serious distress during the twenty-six days of the paroxysm. In spite of the long duration of the attack there were no signs of heart failure. There is a general impression that a severely injured heart cannot long maintain a ventricular rate of 150 to 200. However, Fishberg¹⁷ emphasizes that in a vast majority of attacks of paroxysmal tachycardia, even in those with a rate above 200, there are no signs of circulatory failure. After cessation of the attack the electrocardiogram showed the characteristic tracing of posterior myocardial infarction. The occurrence of ventricular tachycardia with myocardial infarction is not uncommon, but it is usually associated with a recent myocardial lesion. In Case 1, however, the clinical and laboratory findings did not give evidence of acute myocardial lesion. The temperature, sedimentation rate, and white blood count were normal. It seems probable, therefore, that the sensitization of ventricular foci by the excessive use of digitalis was responsible for the attack. It is well known that a small dose of digitalis taken over a long period of time may produce a more severe intoxication than a large dose taken for a short time.

In Cases 2 and 3 there was no evidence of cardiac damage. No cause for the attacks could be found, except possibly in Case 3, where an increase in frequency and duration of the attacks was associated with the premenstrual cycle. The patients were 39 and 38 years of age, respectively. Both were able to continue their work after the tachycardia subsided. The electrocardiogram taken after the cessation of the attack in Case 2 showed inverted T waves in Lead I and in the chest leads, and that taken in Case 3 showed inverted T waves in Leads II and III. It was interesting to note that after the attack not only did the T waves in Lead I and in the chest leads become inverted, but the R wave

ELECTROCARDIOGRAPHIC STUDIES DURING AND AFTER PNEUMOCOCCUS PNEUMONIA

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REPORTED studies show that pneumonia may be accompanied by electrocardiographic deviations from the "normal."^{1-4, 6} These include changes in the heart rate and rhythm as well as significant variations in the P wave, T wave, RS-T segment, and various components of the QRS complex. The recorded incidence of such changes has varied widely, apparently depending on such factors as selection of cases, severity of pneumonia, time of study in relation to the course of the disease, and length of observation. The reported incidence of T-wave inversion in Leads I and II of the electrocardiogram has varied between 2.4 per cent³ and 27.1 per cent.⁶ Significant P-R interval prolongation has varied between 6.9 per cent³ and 35 per cent.² In some instances, the electrocardiographic changes were such that they were interpreted as being due to myocardial disease.^{2-4, 6} The electrocardiographic studies reported thus far have been based almost entirely on tracings obtained from the standard leads.

In this study, which is a part of a general study of the circulation in pneumococcus pneumonia,⁷ the precordial Lead IVF⁸ was recorded as well as the standard limb leads. Serial electrocardiograms including standard and chest leads were made routinely on pneumonia patients upon admission to the hospital and at frequent intervals during the disease and after recovery. Each record was taken with the patient in the supine position at an angle of about 30 degrees with the horizontal. In order to keep the chest electrode at a constant point for serial examinations, its position was marked by the intracutaneous injection of the blue dye, T-1824, which remains at the site of injection for several weeks.

This report is based upon a study of 449 electrocardiograms. Four hundred and thirty of these tracings were made on 82 patients who survived pneumonia and who had at least one electrocardiogram taken during the disease and one after recovery (the number per patient varied between two and 16). Nineteen of the electrocardiograms were made on 10 patients who died of pneumonia. Each of the patients in the study had pneumococcus pneumonia, proved bacteriologically by study of sputum and blood. In each instance the clinical diagnosis and location of the pulmonary lesion was confirmed by x-ray or autopsy. It is emphasized that these cases differ somewhat

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Use of the term "pneumonia" in this paper with reference to the observations of the authors is restricted to the disease pneumococcus pneumonia.

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fact Paul White¹⁸ emphasizes that "it is simpler, safer, and probably almost as effective to give quinidine by mouth." Our experience in this case and that of others in recently reported cases seems to indicate that a large, single dose is more useful than a great amount of quinidine given in smaller doses over a longer period of time.

SUMMARY

Four cases of paroxysmal ventricular tachycardia are reported. One attack lasted for twenty-six days without interruption and, although associated with myocardial infarction, ended with complete recovery after oral administration of a large, single dose of quinidine sulfate. Another attack, which showed bidirectional ventricular complexes due to digitalis intoxication, was treated in this manner, and recovery followed. In two of the four cases there was no evidence of organic heart disease.

The electrocardiographic changes associated with and following a paroxysm of ventricular tachycardia are discussed.

The advantage of oral administration of a large, single dose of quinidine sulfate is emphasized.

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Changes in axis deviation occurred in a few instances. The electrocardiographic changes other than significant T-wave changes are summarized in Table I.

Changes in the T waves were noted on admission in 35 of 82 patients (42.7 per cent) who survived pneumonia, and in five of the 10 patients who

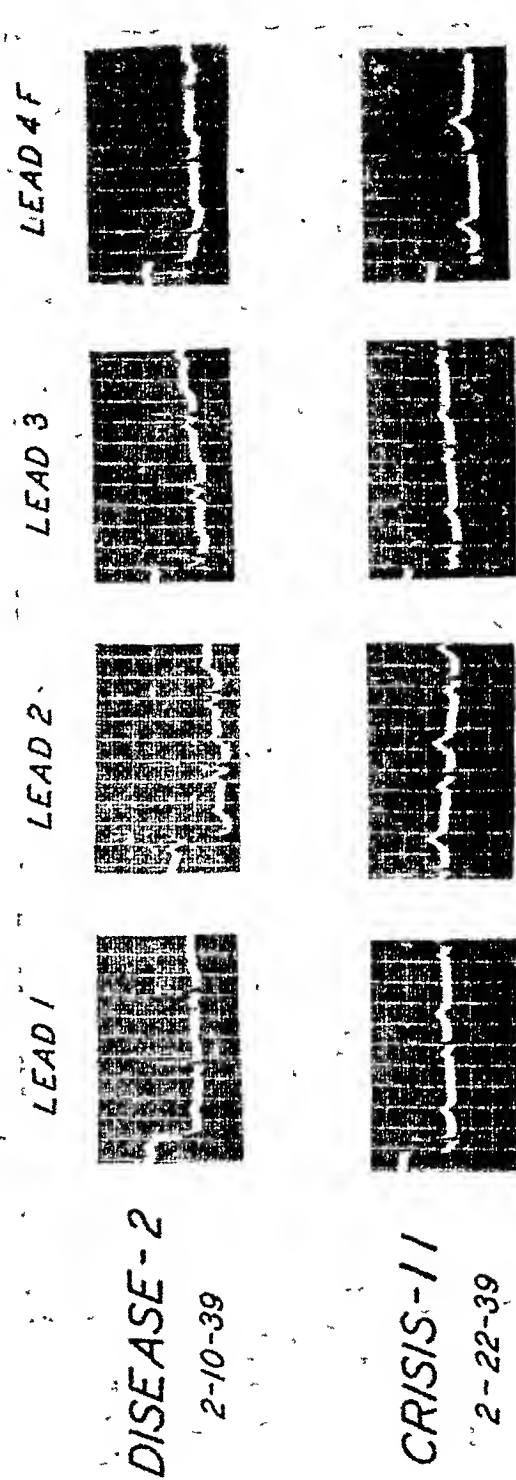


Fig. 1.—Woman, aged 50 years. Electrocardiograms taken on the second day of pneumococcus pneumonia, Type VII, and eleven days after crisis. No bacteremia. Right middle lobe involved. History of angina pectoris.

died (Table II). These changes consisted chiefly of low amplitude T waves (2 mm. or less), or inversion of the T waves, or both, in Leads I, II, and IVF (Table III). Deviations in T_3 alone were not considered significant in this study. In the 12 patients in whom the T-wave changes persisted upon recovery

from those previously reported in the literature in that most were seen early in the course of pneumonia, the average duration of disease at the time of admission being three days; and each was treated by either type-specific anti-pneumococcus serum, or chemotherapy, or both. The total febrile course was characteristically short, averaging slightly over four days in those cases in which the onset of disease and the crisis could be precisely defined. These factors may account, in part, for the discrepancies between previous observations and those reported here.

The following patients were excluded from the study: all those with single electrocardiographic observations; four who, during intravenous therapy, developed electrocardiographic abnormalities which persisted on recovery from pneumonia and were thought to be a result of such therapy⁸; and two patients who, during pneumonia, developed electrocardiographic changes which persisted on recovery and were associated with clinical and laboratory manifestations of acute rheumatic fever. Included in the group are those patients who developed temporary electrocardiographic changes during intravenous therapy which apparently were unrelated to the pneumonia. These temporary alterations associated with intravenous therapy are, however, not included as changes due to pneumonia and have been reported elsewhere.⁹ Digitalis was administered to two patients. Both died and are included in the series of fatal cases.

Although in this study the most striking changes occurred in the T waves, other minor electrocardiographic deviations, such as sinus tachycardia, post-critical bradycardia, and insignificant changes in the RS-T segment were encountered. The RS-T segment changes usually consisted of deviation from the base line of 1 mm. or less. Disturbances in the basic cardiac rhythm were not observed during the course of pneumonia. A significantly abnormal P-R interval, that is, a P-R that was greater than 0.21 second or one that showed a change of ± 0.04 second in serial tracings, was not observed in any patient.

TABLE I. ELECTROCARDIOGRAPHIC CHANGES OTHER THAN T-WAVE CHANGES IN NINETY-TWO PATIENTS DURING PNEUMOCOCCUS PNEUMONIA

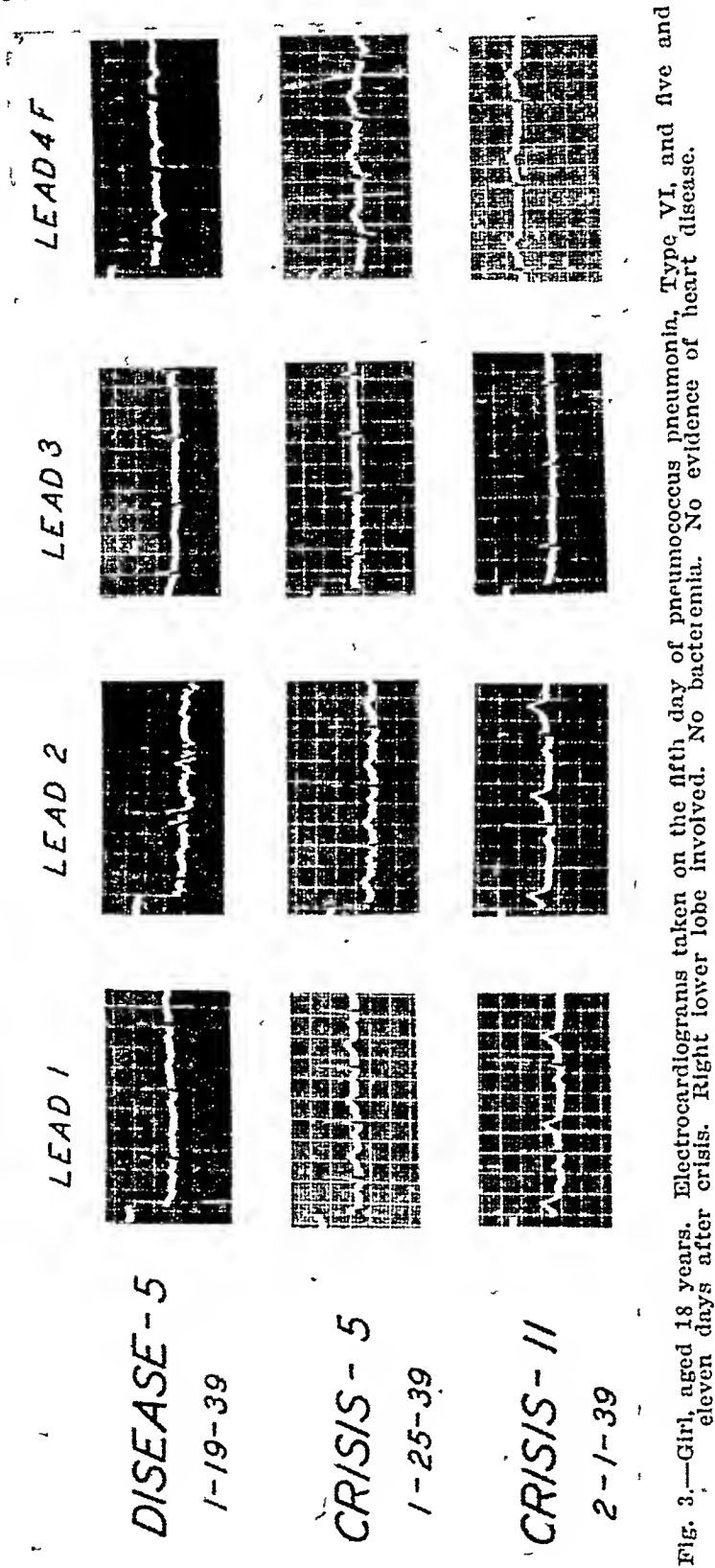
	RECOVERED		DIED	
	NUMBER	PER CENT	NUMBER	PER CENT
Tachycardia (rate > 125)	12	14.7	4	40.0
Postcritical bradycardia (rate < 60)	8	9.8	—	—
P-R interval > 0.21 second or change ± 0.04 second	—	—	—	—
Change in RS-T interval ± 1 mm. or less	9	11.1	1	10.0
Change in axis deviation*	17	20.7	—	—
Total cases observed	82	100.0	10	100.0

*Toward right during pneumonia (11 cases; 13.4 per cent); toward left during pneumonia (6 cases, 7.3 per cent).

TABLE II. INCIDENCE OF T-WAVE CHANGES IN NINETY-TWO PATIENTS WITH PNEUMOCOCCUS PNEUMONIA AT THE TIME OF ADMISSION TO HOSPITAL ACCORDING TO OUTCOME OF THE DISEASE

	NUMBER			PER CENT	
	TOTAL	T-WAVE CHANGE	NO T-WAVE CHANGE	T-WAVE CHANGE	NO T-WAVE CHANGE
Recovered—no permanent change	70	23	47	57.5	90.4
—permanent T-wave change	12	12	—	30.0	—
Died	10	5	5	12.5	9.6
Total cases observed	92	40	52	100.0	100.0

Figs. 1 to 4 illustrate characteristic examples of the transient electrocardiographic abnormalities encountered in pneumonia. It will be noted that although T-wave inversions occurred they were not accompanied by significant



alterations in the RS-T segment. Furthermore, the trend of T-wave changes which occurred during the course of pneumonia was consistent and followed a definite pattern; during the acute phase of the disease the T waves were flat

from pneumonia, it is believed that underlying myocardial disease was their cause. However, in 23 (28.1 per cent) of the patients who survived pneumonia, electrocardiographic changes suggestive of "myocardial disease" occurred during the disease and disappeared during recovery. In no instance did a pneu-

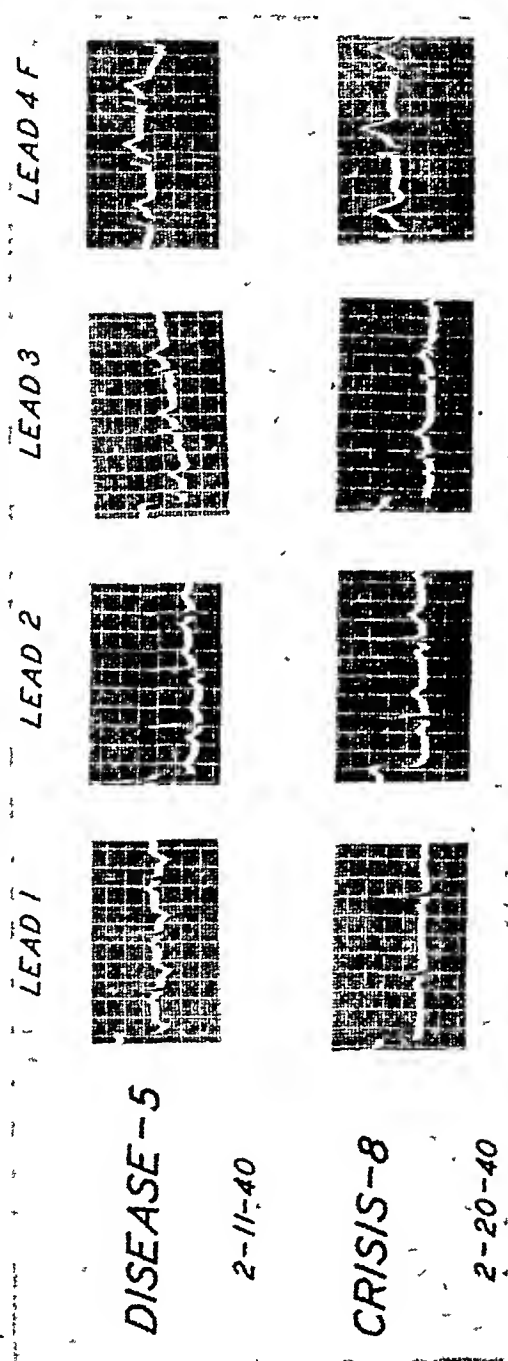


Fig. 2.—Woman, aged 62 years. Electrocardiograms taken on the fifth day of pneumococcus pneumonia, Type II, and eight days after crisis. No bacteremia. Right and left lower lobes involved. Pleural effusion developed at left base on twelfth day after crisis.

monia patient with a normal electrocardiogram at the time of admission to the hospital develop transient T-wave changes of the type here described while under observation.

and are included in the group of recovered patients having permanent electrocardiographic changes.

One patient was observed during two attacks of lobar pneumonia involving the right upper lobe (Figs. 6A and 6B). During the first attack a Type I

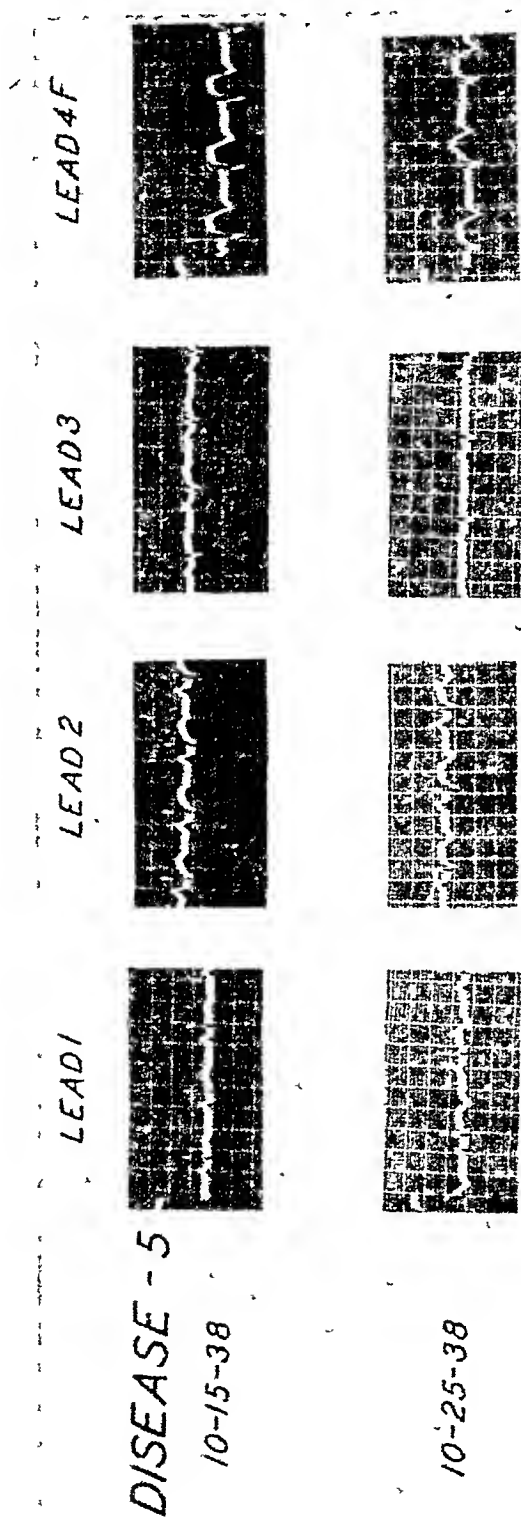


Fig. 5.—Man, aged 58 years. Electrocardiograms taken on the fifth and fifteenth days of pneumococcus pneumonia, Type VII. Right lower lobe involved. No bacteremia. Acute anterior myocardial infarction. Note significant changes in RS-T segment in contrast to changes observed in the electrocardiograms in Figs. 1, 2, 3, 4, and 6.

Pneumococcus was recovered from the sputum; during the second attack a Type VIII *Pneumococcus* was recovered from both sputum and blood. The first attack was treated with Type I antipneumococcus rabbit serum; the second attack was

or inverted; and as the patients recovered from their disease the T waves returned toward, or to, normal.

Two patients developed classic evidence of acute myocardial infarction during pneumonia. The electrocardiograms of one of them are shown in Fig.

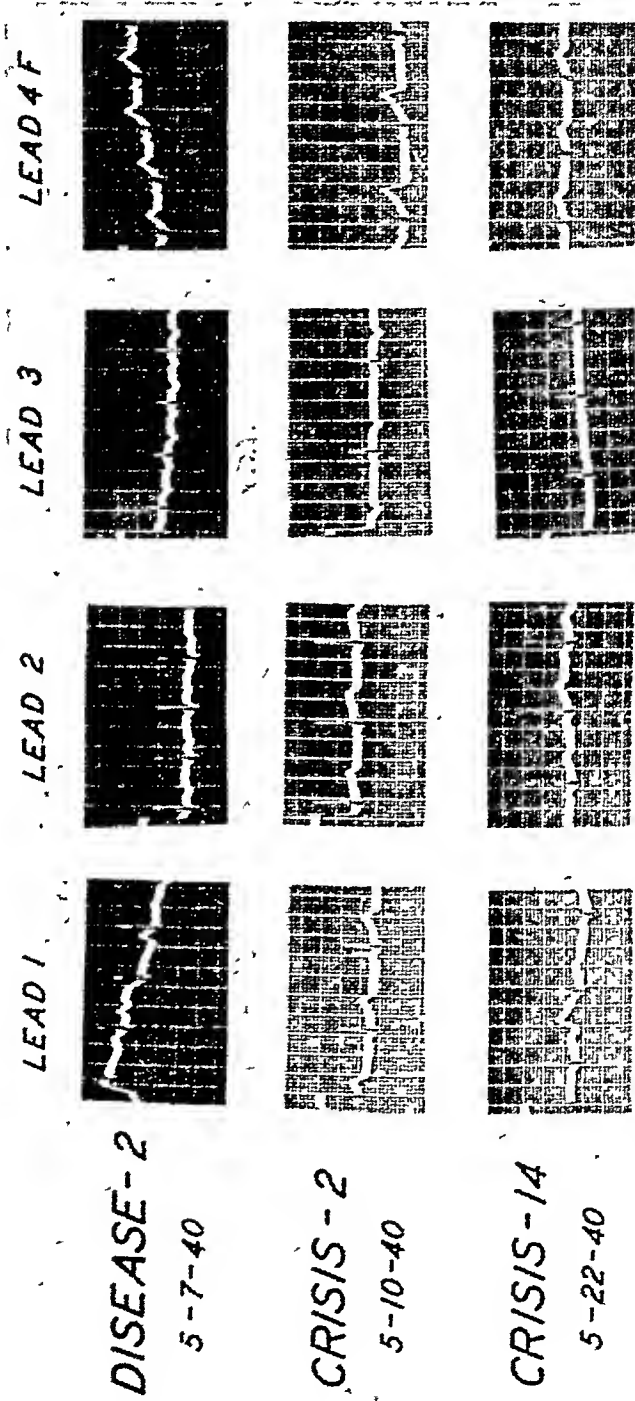


Fig. 1.—Boy, aged 11 years. Electrocardiograms taken on the second day of pneumococcus pneumonia, Type I, and two and fourteen days after crises. Right lower lobe involved. No bacteremia. No evidence of heart disease.

5 to emphasize the contrast between this electrocardiographic pattern and that due to pneumonia alone, particular emphasis being placed on the lack of significant RS-T segment change in the latter. Both patients recovered

In order to determine what factors might induce transient electrocardiographic changes in some cases of pneumonia but not in others, various possible factors, including age, sex, type of pneumococcus, bacteremia, occurrence of pleural fluid, location of lesion, chest pain, heart rate, and the presence of pre-

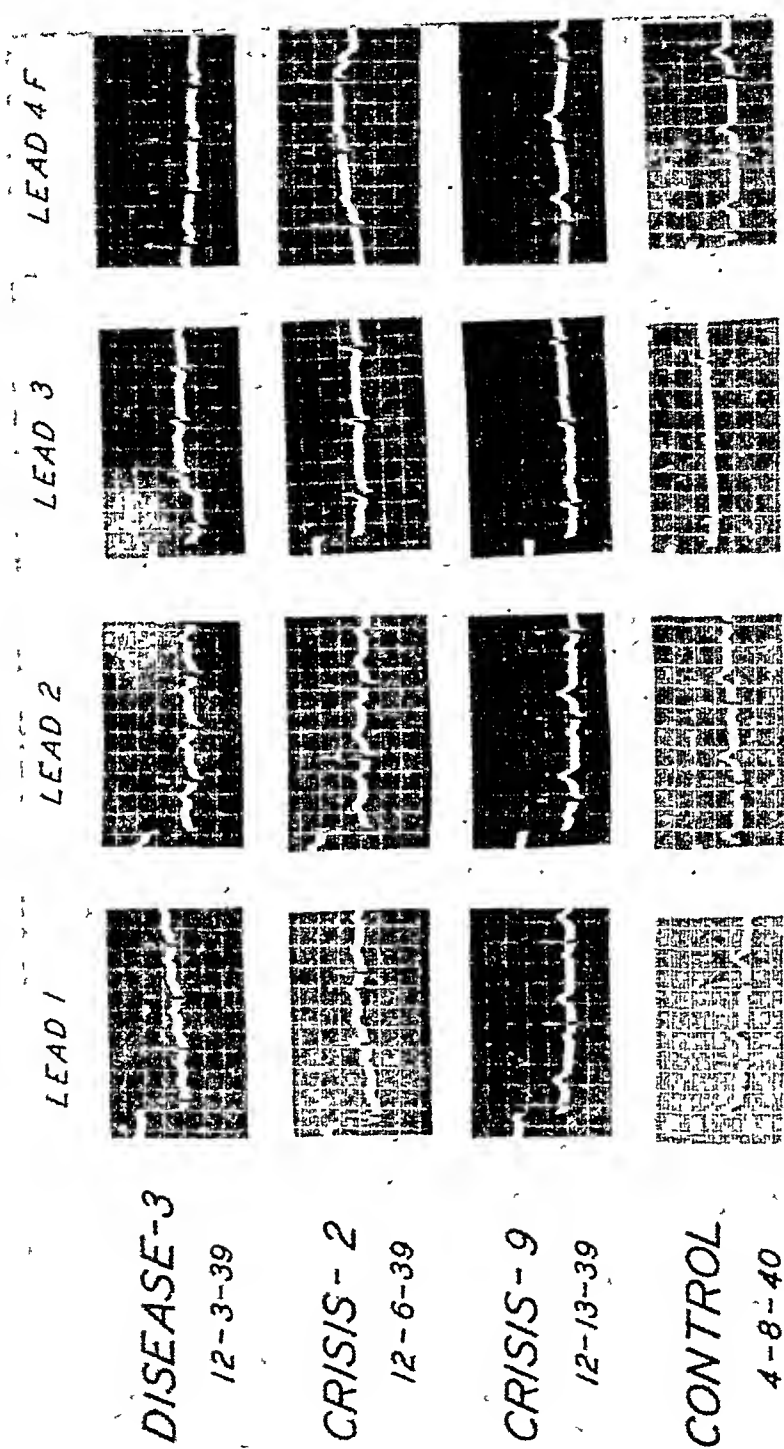


Fig. 6B.—The second attack was caused by pneumococcus Type VIII. Bacteremia present. No evidence of heart disease. Note the identical electrocardiographic changes during each attack of pneumonia with return to normal on recovery.

existing cardiovascular disease, were analyzed. These are summarized in Table V. Except possibly for age, no significant correlation could be demonstrated. It is of interest to note that T-wave changes occurred most frequently in relatively young individuals who presented no other evidence of cardiovascular disease. Of 23 patients showing transient electrocardiographic changes

treated with oral sulfapyridine (total dose 24 Gm). It is of interest to note that similar deviations in the electrocardiogram occurred during both attacks of pneumonia and that there was a return to normal on recovery in each instance.

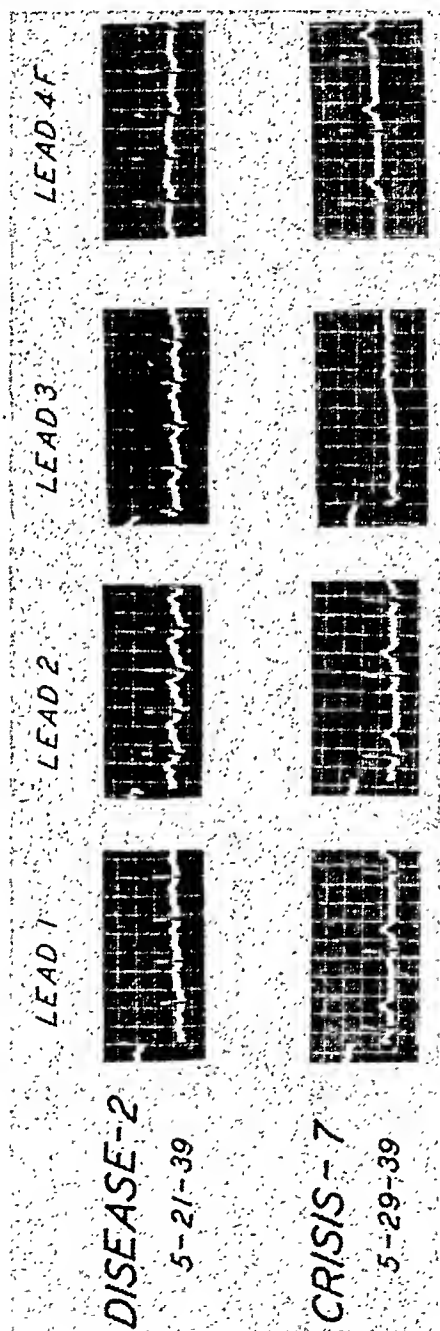


FIG. 6A.—Woman, aged 38 years. Electrocardiograms taken during two attacks of pneumococcus pneumonia involving the right upper lobe. A, The first attack was caused by pneumococcus Type 1. No bacteremia.

Table IV summarizes the specific therapy employed in the recovered cases. It will be seen that the electrocardiographic changes are independent of the types of treatment employed: type-specific antipneumococcus serum, sulfonamide given orally or parenterally, or combinations of these forms of therapy.

TABLE V. T-WAVE CHANGES OCCURRING IN EIGHTY-TWO RECOVERED CASES OF PNEUMOCOCCUS PNEUMONIA ACCORDING TO CERTAIN FACTORS IMPORTANT IN PNEUMONIA

	TOTAL	T-WAVE CHANGES					
		NUMBER			PER CENT		
		TRAN- SIENT	PERMA- NENT	NONE	TRAN- SIENT	PERMA- NENT	NONE
<i>Age</i>							
Less than 40 years	38	15	4	19	65.2	33.3	40.4
40 years and over	44	8	8	28	34.8	66.7	59.6
<i>Sex</i>							
Male	40	13	5	22	56.5	41.7	46.8
Female	42	10	7	25	43.5	58.3	53.2
<i>Pneumococcus Type</i>							
Common (I, III, V, VII, and VIII)	44	14	8	22	60.9	66.7	46.8
Other types	38	9	4	25	39.1	33.3	53.2
<i>Bacteremia</i>							
Present	15	6	3	6	26.1	25.0	12.8
Absent	67	17	9	41	73.9	75.0	87.2
<i>Pleural Fluid</i>							
Present	9	5	1	3	21.7	8.3	6.4
Absent	73	18	11	44	78.3	91.7	93.6
<i>Location of Lesion in Lung</i>							
Right only	53	13	10	30	56.5	83.3	63.8
Left only	21	6	2	13	26.1	16.7	27.7
Both	8	4	—	4	17.4	0.0	8.5
<i>Chest Pain</i>							
Present	64	18	8	38	78.3	66.7	80.9
Absent	16	4	4	8	17.4	33.3	17.0
Not known	2	1	—	1	4.3	0.0	2.1
<i>Heart Rate</i>							
Under 125	70	20	11	39	87.0	91.7	83.0
125 and over	12	3	1	8	13.0	8.3	17.0
<i>Pre-existing Cardiovascular Disease</i>							
Present	6	2	2	2	8.7	16.7	4.3
Absent	68	19	7	42	82.6	58.3	89.3
Uncertain	8	2	3	3	8.7	25.0	6.4
Total recovered cases	82	23	12	47	100.0	100.0	100.0

patients in this group (total dose 0.5 and 0.7 Gm., respectively) the changes in their electrocardiograms were not characteristic of digitalis effect and the autopsy findings (in them) were not significantly different from the autopsy findings in patients who had not received digitalis.

The appearance of such T-wave changes as are here described raises the question of whether or not they represent evidence of "myocarditis." Autopsy studies of the hearts, of pneumonia patients, made before 1917, were reviewed by Cohn and Jamieson.¹ These failed to show the presence of significant myocardial changes in pneumonia and led the authors to state: "Of the pathologic histology of the heart in pneumonia there is still insufficient knowledge, but it does not appear that extensive alterations occur. Anatomical lesions are according to these investigations infrequent and on the whole insignificant." In contrast, Stone¹⁰ more recently reported observations on 34 cases of lobar pneumonia in which abnormalities in the myocardium were found in 79.4 per cent, by histologic examination. Included in the pathologic diagnoses were "parenchymatous degeneration" (52.9 per cent), "fatty degeneration" (11.7 per cent), "leucocytic and round-cell infiltration" (8.9 per cent), "hyaline degeneration" (2.9 per cent), and "interstitial myocarditis" (2.9 per

TABLE III. T-WAVE CHANGES IN NINETY-TWO PATIENTS WITH PNEUMOCOCCUS PNEUMONIA

	RECOVERED		DIED (5 PATIENTS)
	TRANSIENT CHANGES (23 PATIENTS)	PERMANENT CHANGES (12 PATIENTS)	
Low voltage T ₁	11	4	4
Low voltage T ₂	8	3	2
Low voltage T ₄	1	0	0
Inverted T ₁	1	1	0
Inverted T ₂	4	1	1
Inverted T ₄	3	1	1
Diphasic T ₁	0	2	0
Diphasic T ₂	0	0	0
Diphasic T ₄	6	5	0

TABLE IV. SPECIFIC THERAPY IN EIGHTY-TWO RECOVERED CASES OF PNEUMOCOCCUS PNEUMONIA

TREATMENT	NUMBER OF CASES TREATED	NUMBER OF CASES SHOWING TEMPORARY T-WAVE CHANGES DURING PNEUMONIA
Serum alone	30	7
Sulfonamide alone	31	8
Both serum and sulfonamide	21	8
Serum alone or with sulfonamide	51	15*
Sulfonamide alone or with serum	52	16†
Total recovered cases	82	

*Of these, nine received horse serum, five received rabbit serum, and one received both horse and rabbit serum.

†Of these, 13 received sulfapyridine (total dose ranging from 8 to 52.5 Gm.); two received sulfathiazole (total dose 20 and 25.5 Gm.); and one received both drugs. Sulfonamides were administered by intravenous route in nine cases; sodium sulfapyridine, in eight cases (dose range 3.8 to 7.6 Gm.); and sodium sulfathiazole in one case (dose 3 Gm.).

during pneumonia, 15 (65.2 per cent) were under 40 years of age. The average age for the group was 37 years. In contrast, of 47 patients who did not show any electrocardiographic changes during pneumonia, 28 (59.6 per cent) were over 40 years of age. The average age in this group was 44 years. In the cases with transient electrocardiographic changes, the duration of the pneumonia at the time the first electrocardiogram was taken was 2.9 days, and in those without such changes, it was 3.1 days. Anoxia in the two groups will be discussed later.

Finally, the autopsy material was studied to determine whether or not pathologic evidence of myocardial change accompanied the electrocardiographic abnormalities found in the fatal cases. Nine of the ten fatal cases of pneumonia on whom electrocardiographic studies were made came to autopsy. Five of these showed abnormal electrocardiograms which did not differ appreciably from those found in the patients who recovered (Table III). The incidence of abnormal electrocardiograms likewise was essentially the same in the fatal and nonfatal cases (Table II). In the four patients without electrocardiographic changes and in four of the five patients with abnormal electrocardiograms, there was no significant gross or microscopic evidence of heart disease. In one patient, in whom the electrocardiogram showed inverted T waves in Leads II and III, an acute fibrinous pericarditis was found which could have accounted for the T-wave changes. Although digitalis was given to two

Certain factors which are considered of importance in pneumonia and which might be associated with the electrocardiographic abnormalities encountered in this study were analyzed. Such analysis failed to show positive correlation between T-wave changes and bacteremia, location of lung lesion, presence or absence of pleural fluid, chest pain, or duration of disease (Table V). Although fever has been reported as a cause of electrocardiographic deviations somewhat similar to those reported here,¹⁵ our data showed no differences in the febrile response between the patients with and those without electrocardiographic changes. The patients showing electrocardiographic changes had a mean temperature of 103° F. at the time the admission electrocardiogram was taken, whereas those showing no electrocardiographic changes had a mean temperature of 102.9° F. at the time the admission electrocardiogram was taken.

It seemed possible that circulatory changes, such as increased plasma volume,⁷ which are known to occur during pneumonia, might play a role in the production of transient T-wave changes by placing an additional burden on the heart. Analysis of these data,⁷ however, showed that in twelve patients with T-wave changes during pneumonia the mean increase in plasma volume during pneumonia was 272 c.c. (13 per cent), whereas in twenty-four patients in whom such electrocardiographic changes did not occur during pneumonia the mean increase in plasma volume was 328 c.c. (11.4 per cent).

The altered electrolyte balance in pneumonia, particularly the shifts in sodium and potassium concentration, may also play a role. No data are available from this study to support or refute this possibility.

Various investigators have pointed out the serious prognostic significance in pneumonia of certain electrocardiographic changes, particularly low voltage T waves and T wave inversion. Master, Romanoff, and Jaffee² stated that "negative T waves may be significant of an extremely toxic and fatal pneumonia" and, to substantiate this view, reported a mortality of 40 per cent in a group of patients with such changes, in contrast with a mortality of 17 per cent in a control group. Bullowa and Lowen,⁶ supporting this contention, reported a 46 per cent mortality in cases with flat or inverted T waves, in contrast with a 10 per cent mortality in a group of pneumonia patients who did not show this change. Bellet and McMillan⁵ expressed the opinion that, in pneumonia, manifestations of severe myocardial derangement, such as T-wave inversion, indicated a poor prognosis. In this study, however, alterations in voltage, or even inversion of the T waves in Leads I, II, and IVF, with or without minor RS-T segment changes, when due to pneumonia, were not found to be of serious prognostic importance in a group of patients with pneumonia who were treated adequately (Table II).

Although this study has not thrown light on the mechanism of production of the transient T-wave changes which occur during pneumonia, it is important to recognize that T-wave changes such as are here described may accompany pneumonia, disappear on recovery from this disease, and not be due to significant structural changes in the myocardium. This fact is of importance

cent). The significance and interpretation of such changes, however, are open to question and are not supported by the autopsy findings in the present study.

The observation that myocarditis may be associated with sulfonamide administration^{11, 12} focuses attention on the possible role played by sulfonamide therapy in the production of the type of electrocardiographic changes which were observed in this study. Analysis of the cases failed to show a preponderance of electrocardiographic changes in the sulfonamide-treated cases as compared with the nonsulfonamide-treated cases (Table IV). Against a relationship between the drug and the electrocardiographic changes is the fact that in this study abnormal electrocardiograms were found in the patients at the time of admission to the hospital, before sulfonamides were administered. Furthermore, the administration of these drugs did not appear to alter the subsequent course of the electrocardiogram. Finally, in the nine fatal cases with electrocardiographic changes which came to autopsy, eight of which received one or more of the sulfonamide drugs, evidence of myocarditis, as described by French and Weller,¹¹ was lacking. It is not possible, therefore, to ascribe the electrocardiographic changes which were found in pneumonia in this study to recognizable structural abnormalities of the myocardium which were a result of either pneumonia or sulfonamide administration.

Since anoxia is capable of producing T-wave changes similar to those reported here,¹³ blood-gas studies were made to obtain information on this point. At the same time that electrocardiograms were taken (on admission and after recovery) arterial oxygen content and capacity were determined in 33 cases, and arterial carbon dioxide content was determined in 32 cases. The mean arterial oxygen saturation during pneumonia was somewhat reduced, being 92.1 per cent in patients showing transient T-wave changes and 89.9 per cent in those without such electrocardiographic changes. Individual cases, however, showed considerable variation: from 78.3 per cent to 101 per cent in those with transient T-wave changes, and from 91.4 per cent to 99.3 per cent in the cases without such electrocardiographic changes. Similarly, the arterial carbon dioxide content did not show significant differences in the two groups: in the patients who showed transient T-wave changes it varied from 31.4 to 51.3 volumes per cent, with a mean of 42.2 volumes per cent; in those without such electrocardiographic changes it varied from 33.5 to 55.3 volumes per cent, with a mean of 43.5 volumes per cent. After recovery from pneumonia, both the oxygen saturation and the carbon dioxide content of the arterial blood in both groups were usually slightly, but about equally, increased as compared with the determinations made during the course of pneumonia. These observations lend little support to the concept that anoxia is causally related to the T-wave changes which occur during pneumonia. In this regard, however, the observation of May,¹⁴ that the more normal the myocardium the more susceptible it is to induced anoxia (as evidenced by T-wave change), is of speculative interest. It has already been emphasized that the patients in this study who showed transient T-wave changes in the electrocardiogram were for the most part relatively young, and free from cardiovascular disease (Table V).

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in assessing the cardiac status of patients who present evidences of acute pulmonary infection and electrocardiographic abnormalities such as have been described. In the absence of "classic" electrocardiographic evidence of myocardial infarction, electrocardiograms taken during pneumococcus pneumonia must be interpreted with caution and with due consideration of the changes which pneumonia per se may produce. The final diagnosis of the cardiac status of such patients must await interpretation of postrecovery electrocardiograms. Failure to do this may lead to erroneous diagnoses of "myocardial disease."

SUMMARY AND CONCLUSIONS

1. Deviations from normal are frequently found in electrocardiographic tracings taken during pneumococcus pneumonia.

2. T-wave changes of sufficient degree to suggest "myocardial disease" occurred in 35, or 43 per cent, of a carefully studied group of 82 patients who survived pneumococcus pneumonia. In 23 patients, or 28.1 per cent of the total group, these changes followed a definite pattern during the disease and disappeared on recovery.

3. Post-mortem examination of the hearts of nine patients who died of pneumococcus pneumonia showed no significant structural abnormality, even though four of these showed T-wave changes in the electrocardiogram. In one patient whose electrocardiogram showed T-wave inversion an acute fibrinous pericarditis was present.

4. Flat, low-voltage, or inverted T waves in Leads I, II, or IVF, without significant S-T changes, occurring during, and related to the pneumonia, are not of serious prognostic importance if the pneumonia is diagnosed early and treated adequately.

5. Recognition of the occurrence of transient T-wave changes in pneumococcus pneumonia may be of importance in the differential diagnosis of pneumococcus pneumonia and myocardial disease in patients in whom clinical evidence is not definitive.

6. The possible causes of such electrocardiographic changes are discussed.

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the site of involvement. Leaflet depositions appeared as spotty areas which were irregularly placed in the region of the mitral valve, in contrast to the continuous bandlike depositions indicating annulus fibrosus involvement. The major difficulty encountered was in distinguishing lighter ring deposits from spotty leaflet involvement. Nevertheless, this technique is more precise than fluoroscopic examinations in vivo, and is far more accurate for detecting minimal calcium deposits than is gross pathologic observation. The pathology protocols and clinical records were then reviewed, and the desired data were tabulated. Since the coronary arteries were injected and dissected,¹⁶ the data pertaining to pathology in the coronary arteries, as well as to calcification in the mitral valve, are considered highly accurate. The "T" test was used in analyzing these data; the results, as given, are significant.

RESULTS

Calcification in the mitral valve was found in 78 hearts, and in approximately one-half of these the aortic valve was similarly involved. The annulus fibrosus was the most frequent site of calcification in the mitral valve, and was involved in 70 of the 78 hearts; in 6 of these there was concomitant calcification of the mitral leaflets. Calcification of the leaflets alone was noted in only 8 hearts. Deposition of calcium occurred almost equally in the anterior and posterior leaflets, while calcification of the annulus fibrosus was more frequently posterior than anterior (Table I). Calcification of the mitral valve was found twice as often in women as in men (Table II), despite a 3:2 ratio of male hearts to female hearts in the entire group of 766 hearts.

TABLE IA. SEX, AGE, HEART WEIGHT, AND LOCATION OF CALCIFICATION IN SEVENTY-EIGHT CASES WITH MITRAL VALVE CALCIFICATION

	NUMBER OF CASES	SEX*		AGE (YRS.)		HEART WEIGHT (GRAMS)	
		M.	F.	RANGE	AVERAGE	RANGE	AVERAGE
I. <i>Mitral Valve Alone</i>							
1. Annulus alone	29	6	23	35-83	70	268- 900	452
2. Annulus and leaflets	2	1	1	45-61	53	390- 600	495
3. Leaflets alone	5	3	1	28-52	40	510- 825	664
4. Total	36	10	25	28-83	66	268- 900	481
II. <i>Mitral and Aortic Valves</i>							
1. Annulus alone (mitral)	35	13	22	44-83	67	180- 780	448
2. Annulus and leaflets (mitral)	4	1	3	28-68	54	350- 560	468
3. Leaflets alone (mitral)	3	2	1	16-68	51	350-1,100	683
4. Total	42	16	26	16-83	65	180-1,100	468
III. <i>Groups I and II Combined</i>							
1. Annulus alone	64	19	45	35-83	69	180- 900	450
2. Annulus and leaflets	6	2	4	28-68	54	350- 600	477
3. Leaflets alone	8	5	2	16-68	44	350-1,100	671
Grand total	78	26	51	16-83	65	180-1,100	470

*Not stated in one case.

TABLE IB: Location of Calcification on Annulus and on Leaflets of Mitral Valve

	ANNULUS	LEAFLET
Anterior	11	5
Posterior	30	6
Anterior and posterior	29	3

CALCIFICATION OF THE MITRAL VALVE

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THE frequent observation by roentgenologists and pathologists of calcification in the region of the mitral valve has led to much conjecture concerning its origin and significance. Views regarding its etiology may be divided into three general groups: inflammation, degeneration, and metabolic disturbances. Calcification of the mitral ring has been ascribed to degenerative^{1, 7, 8, 10, 11} or atheromatous processes^{2, 3} of nonrheumatic origin⁶⁻¹¹ occurring chiefly in the aged.^{2, 4, 5, 7, 8, 10, 11} It has been pointed out that the lesion occurs at the site of maximum stress and strain¹ and that decreased blood supply is an important factor in its genesis. Others have suggested a similarity to the Mönckeberg type of aortic valve calcification,^{12, 13} assuming a predilection to collagen involution with deposition of lipoid and calcium.¹² The acellular structure of the posterior portion of the annulus is held responsible for localization of calcification in that part of the ring.²⁰ Many investigators are of the opinion that calcification of the annulus fibrosus of the mitral valve is of no clinical significance. On the other hand, calcification of the leaflets of the mitral valve has been considered inflammatory (rheumatic) in origin, when it occurs in younger age groups.^{3, 6, 7, 9, 10}

Decreasing the caloric intake in rats has been found to result in increased calcium deposition in the heart, the aorta, and the kidneys.¹⁴ Animal experimentation has also shown that the form of mineral supplement has an effect upon the production of cardiac calcification, but that moderate enforced exercise reduces the incidence of calcification.¹⁵ The present investigation was undertaken to determine the incidence and distribution of calcification on the mitral valve and to evaluate its clinical significance.

METHOD OF STUDY

Seven hundred sixty-six unselected hearts, prepared by the Schlesinger technique,¹⁶ were used. There is no overlapping of the valve rings and leaflets of the "completely unrolled hearts" prepared by this method, and roentgenograms of these specimens are ideally suited for the detection of areas of calcification which might be overlooked by other methods of examination. The roentgenograms were examined for valvular calcification without reference to pathologic or clinical data. Calcium deposits were recognized as opaque areas in the region of the valve. These deposits appeared as thick heavy bands, light thin lines, or irregular spotty areas. When the deposition occurred as a straight line, or as a U- or J-shaped configuration, the annulus fibrosus was considered

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TABLE III. INCIDENCE OF VARIOUS CARDIOVASCULAR CONDITIONS IN CASES OF MITRAL VALVE CALCIFICATION IN RELATION TO THE LOCATION OF CALCIFICATION*

	RHEU- MATIC HEART DISEASE	BAC- TERIAL ENDO- CARDITIS	ARTERIO- SCLEROTIC AND HYPER- TENSIVE HEART DISEASE	MYO- CARDIAL INFARC- TION	GENER- ALIZED ARTERIO- SCLEROSIS	MINIMAL AREAS OF CORONARY CALCIFICA- TION
<i>I. Mitral Valve</i>						
1. Annulus alone	2/28	0/28	11/26	5/26	16/27	22/29
2. Annulus and leaflets	0/2	2/2	0/2	0/2	0/2	0/2
3. Leaflets alone	5/5	0/4	0/5	0/3	0/3	1/5
4. Total	7/35	2/34	11/33	5/31	16/32	23/36
<i>II. Mitral and Aortic Valve</i>						
1. Annulus alone	6/35	1/35	9/35	7/33	17/33	26/36
(mitral)						
2. Annulus and leaflets	1/4	1/4	2/4	0/4	2/4	1/4
(mitral)						
3. Leaflets alone	1/2	0/2	1/2	0/2	0/2	0/2
(mitral)						
4. Total	8/41	2/41	12/41	7/39	19/39	27/42
<i>Grand Total</i>	15/76	4/75	23/74	12/70	35/71	50/78

*Discrepancies in the number of cases (denominators) are due to incompleteness of records.

the accepted stigmata of rheumatic heart disease. In all three of these subjects there were hypertension and congestive failure, aortic valve calcification, and extensive coronary disease; the mitral valve calcification involved the annulus as well as the leaflets in two of them. All were women; their ages were 48, 67, and 68 years, respectively. There were, in addition, three other instances of leaflet calcification which were not considered to be rheumatic in origin. These were cases of bacterial endocarditis, two subacute and one acute.

Of 68 cases of mitral valve calcification in which complete pathologic data were available, fifteen, or less than one-fourth displayed no additional cardiac disease other than calcification of the aortic valve, which was present in 10 cases (Table IV). The calcification of the mitral valve in these cases was limited to the annulus fibrosus. In all but 5 cases, however, there was generalized extracardiac vascular disease, i.e., either arteriosclerosis or hypertension. None had angina pectoris. Congestive heart failure was diagnosed clinically in 4 cases, but the diagnosis was questionable in all of them. A clinical diagnosis of heart disease was made in only 5 of the 15 patients. Of the 5 cases with neither important cardiac nor generalized vascular disease, 3 had calcification of both valves and 2 had calcification of the mitral valve alone. In none of the 5 was there angina pectoris or congestive failure, and in none was a clinical diagnosis of heart disease made; none had murmurs. No cardiac death occurred in this group of 15 patients. Vascular disease was the primary cause of death in 2, and neoplastic disease was the cause of death in more than one-third of the group. One patient died at the age of 44 years, following thyroidectomy, and the remaining 14 patients lived beyond the age of 60 years.

Clinical Features.—Reliable data regarding the presence or absence of murmurs were recorded in 53 cases. A murmur was noted in 36, or approx-

TABLE II. RELATION BETWEEN LOCATION OF MITRAL CALCIFICATION, AVERAGE LIFE SPAN, AND AVERAGE HEART WEIGHT

	MALES			FEMALES		
	NUMBER OF CASES	AGE (YRS.)	HEART WEIGHT (GRAMS)	NUMBER OF CASES	AGE (YRS.)	HEART WEIGHT (GRAMS)
I. <i>Mitral Valve Alone</i>						
1. Annulus alone	6	75	427	23	69	460
2. Annulus and leaflets	1	(61)	(390)	1	(45)	(600)
3. Leaflets alone	2	30	668	2	46	690
4. Total	9	63	476	26	66	483
II. <i>Mitral and Aortic Valves</i>						
1. Annulus alone (mitral)	14	67	568	22	68	367
2. Annulus and leaflets (mitral)	1	(74)	(350)	3	47	507
3. Leaflets alone (mitral)	1	(16)	(1,100)	1	(67)	(600)
4. Total	16	65	588	26	66	392
Grand Total	25	64	548	52	66	438

The average life span of the 78 patients whose hearts showed mitral valve calcification did not vary significantly with sex or with associated involvement of the aortic valve (Table II). On the other hand, there was a striking correlation between age and the location of calcification. Thus, calcification of the annulus fibrosus alone occurred most frequently in the group of older subjects, whose life span averaged 69 years; while calcification of the mitral leaflets was noted in a younger group, whose life span averaged 44 years (Table I). The average life span of the group whose hearts showed calcification of both the leaflets and the annulus fibrosus is intermediate between that of either group alone.

The weights of the 78 hearts with mitral valve calcification ranged from 180 to 1,100 grams. Concomitant calcification of the aortic valve did not appear to have a significant influence on heart weight. Hypertrophy was present in most cases, but was greatest in those with calcification of a mitral leaflet. The average weight of 8 hearts with only leaflet calcification was 671 grams, while the average weight of 64 hearts with calcification confined to the annulus fibrosus was 450 grams (Table I). This significant difference may be attributed to the preponderance of rheumatic heart disease in the group with leaflet calcification.

Associated Lesions.—Significant cardiovascular disease, other than calcification, was found in over 75 per cent of the 78 hearts (Tables III and IV). Arteriosclerotic and hypertensive heart disease was present in one-third, rheumatic heart disease in one-fifth, myocardial infarction in one-sixth, and bacterial endocarditis in one-twentieth of the cases. Generalized arteriosclerosis was observed in one-half of the cases, and calcification of the coronary arteries was observed in two-thirds. Calcification of both aortic and mitral valves was not associated with a higher incidence of other cardiovascular lesions than when the mitral valve alone was involved.

In cases of valvular calcification with as well as without other cardiovascular disease, the annulus fibrosus was almost always the site of the calcification in the mitral valve. Even in the 15 rheumatic hearts calcification of the leaflets was noted in fewer than half. Three of the 14 hearts with calcification including the leaflets did not have mitral stenosis and two of these three showed none of

imately two-thirds of these cases; it was apical in 23, aortic in 5, and was heard at both areas in 8. The apical murmur was diastolic in 9 cases; 7 of these were instances of rheumatic heart disease. Eight of the 13 cases with a murmur over the aortic area had aortic in addition to mitral valve calcification, but 5 did not. Murmurs were regularly present in the rheumatic group, but were present in only slightly more than one-half of the nonrheumatic group. They were, however, heard in 70 per cent of the patients with arteriosclerotic and hypertensive heart disease.

The incidence of hypertension, angina pectoris, and congestive failure was not significantly greater in the cases showing calcification of both the aortic and mitral valves than in those with mitral valve calcification alone (Table V). Congestive failure occurred in 60 per cent, hypertension occurred in 38 per cent, and angina pectoris occurred in 16 per cent of the cases. Angina pectoris did not occur in any case with leaflet calcification, but congestive failure was especially common in this group (80 per cent).

Electrocardiograms were available in 29 patients with mitral valve calcification. In only 2 of these, both of whom had bundle branch block, was the calcification a possible factor in producing an abnormal pattern.

TABLE V. HYPERTENSION, ANGINA PECTORIS, AND CONGESTIVE FAILURE IN CASES OF MITRAL VALVE CALCIFICATION*

	HYPERTENSION	ANGINA	CONGESTIVE FAILURE DIAGNOSED
I. <i>Mitral Valve Alone</i>			
1. Annulus alone	12/27	4/27	15/28
2. Annulus and leaflets	0/2	0/2	1/2
3. Leaflets alone	0/4	0/3	3/3
4. Total	12/33	4/32	19/33
II. <i>Mitral and Aortic Valves</i>			
1. Annulus alone (mitral)	12/35	8/35	20/36
2. Annulus and leaflets (mitral)	3/3	0/4	3/4
3. Leaflets alone (mitral)	1/2	0/2	2/2
4. Total	16/40	8/41	25/42
Grand Total	28/73	12/73	44/75

*Discrepancies in the number of cases (denominators) are due to incompleteness of records.

Rheumatic Heart Disease.—The above data indicate that calcification of the mitral valve in rheumatic heart disease may involve the annulus, the leaflets, or both; that leaflet calcification is more frequently found in rheumatic than in nonrheumatic hearts; and that about one-half of the 15 rheumatic hearts showed calcification of the aortic in addition to the mitral valve (Table III).

In the present series the average age (at death) of those with rheumatic heart disease and mitral valve calcification was lower, and the average heart weight was more, than in those with nonrheumatic heart disease. The youngest patient with rheumatic heart disease was 16 years of age; there were areas of minimal calcification on the mitral leaflets and aortic cusps; the heart weighed 1,100 grams and was the largest in this series. The average age of 15 rheumatic patients with mitral valve calcification was 47 years, and the average heart weight was 603 grams, while the average age of 59 patients with non-

TABLE IV. FIFTEEN CASES OF MITRAL VALVE CALCIFICATION WITHOUT ASSOCIATED CARDIAC PATHOLOGY
(FROM SIXTY-SEVEN CASES)*

	AGE (YRS.)	HEART WEIGHT (GRAMS)	GENERALIZED ARTERIO- SCLEROSIS	HYPER- TENSION	MUR- MURS†	ANGINA PECTORIS	CLINICAL DIAGNOSIS OF HEART DISEASE	PRIMARY CAUSE OF DEATH
I. Mitral Ring Alone								
1. Posterior	67 70	370 347	0 +	0 0	0 0	0 0	0 Arteriosclerotic heart disease; auricular fib- rillation; congestive failure	Carcinoma Carcinoma
2. Anterior	79	380	0	0	-	0	0	Diabetes mellitus
3. Anterior and posterior	63 83	330 290	++	0 0	0 0	0 0	0 Congestive failure	Myelogenous leucemia Carcinoma
II. Mitral Ring, Aortic Valve								
1. Posterior (mitral ring)	68 70 65	280 330 335	0 0 0	0 0 +	- 0 Aortic systolic	0 0 0	0 0 Aortic stenosis	Bronchiectasis Mesenteric thrombosis Meningioma
	81 73	340 240	++	0 0	- -	0 0	0 Congestive failure	Meningioma Purulent tracheo bron- chitis
	44	330	0	+	-	0	Congestive failure	Postthyroidectomy hem- orrhage
2. Anterior	73 61	180 380	0 +	0 0	0 0	0 0	0 0	Intestinal obstruction Carcinoma
3. Anterior and posterior	74 78	330 215	++	0 0	- -	0 0	0 0	Cerebral hemorrhage Bronchiectasis

*Pathology data incomplete in eleven cases.

†+ = murmur present; 0 = no murmur present; - = no notation concerning murmur.

DISCUSSION

A new roentgenographic method for ascertaining the presence of mitral valve calcification has been applied to a study of the hearts of 766 unselected patients. This study shows that mitral valve calcification occurred in over 10 per cent of all hearts, and that it was much more common in women than in men. The preponderance of women with mitral valve calcification over men was uninfluenced by the presence of any other associated cardiovascular pathology which we studied. Thus, when aortic valve calcification occurred in combination with mitral valve calcification, as it did in one-half of the cases in this series, the relative frequency of its occurrence in women was nevertheless still much greater than its occurrence in men. The high incidence of women with mitral valve calcification was not due to rheumatic heart disease, which occurred in less than one-fifth of all the cases, particularly since the ratio of the females to males was about the same in this group as in any other division of our cases on the basis of associated pathology. Martens also found the relative incidence of calcification of the mitral ring to be greater among women,¹⁷ and de Oliveira explains this fact by the greater incidence of disturbances in calcium metabolism and of hypertension in women.²⁰

In the entire series, calcification was limited to the annulus in 80 per cent of the cases and to the leaflets in 10 per cent of the cases. Although calcification may occur in any inflammatory lesion, it involved the leaflets in less than one-half of the 15 cases of rheumatic heart disease. Moreover, leaflet calcification was found mostly in the young, and involvement of the annulus was found mostly in the aged; these findings are in agreement with those based upon roentgenographic examination of living subjects.^{6, 7, 10} Seventy-five per cent of the cases with leaflet calcification occurred in rheumatic heart disease or bacterial endocarditis. The high incidence of associated conditions such as generalized arteriosclerosis (in 50 per cent of the cases), coronary artery calcification (66 per cent), and arteriosclerotic and hypertensive heart disease (33 per cent) suggests that calcification in many of these cases may be noninflammatory in nature. A relation between the degree of calcification and age has been noted.¹¹ However, Giese² and Martens¹⁷ were of the opinion that calcification of the mitral ring and that of the blood vessels were unrelated.

Longevity, the incidence of associated lesions, congestive failure, and heart weight were not influenced by the presence of the additional factor of aortic valve calcification. The largest hearts were those with calcification of the mitral leaflets, and occurred mostly in the younger age groups, in patients with rheumatic heart disease. Clinical x-ray examination of hearts with mitral valve calcification similarly reveals a high incidence of hypertrophy in those with leaflet calcification⁶ and similar differences in age and heart size in rheumatic and nonrheumatic heart disease.^{6, 10}

Sohval and Gross¹² were of the opinion that calcification in the heart valves does not appreciably alter the prognosis and bears no apparent relation to heart failure or heart disease, but others have suggested that the mitral systolic murmur may be due to mitral insufficiency produced by calcification of the annulus

rheumatic heart disease and mitral valve calcification was 69 years, and the average heart weight was 436 grams.

In rheumatic heart disease the average life span and average heart weight did not differ significantly in patients who had mitral valve calcification alone and in those who had calcification of both the mitral and aortic valves. These varied, however, with the location of calcification on the mitral valve. The average age at death in nine patients with calcification of the ring was 54 years, and in six with calcification of the leaflets only, 34 years. The average weight of the rheumatic heart in the present series was greater in those with leaflet calcification (719 grams) than in those with calcification of the mitral ring (518 grams). Rheumatic heart disease was the most important factor in the development of congestive failure in the entire series.

In cases with mitral valve calcification, generalized arteriosclerosis, hypertension, myocardial infarction, angina pectoris, calcification of the coronary arteries, and renal disease were less commonly associated with rheumatic than with nonrheumatic hearts. None of the patients with rheumatic heart disease and mitral calcification had myocardial infarction or angina pectoris. Only one had generalized arteriosclerosis, and two had hypertension.

Arteriosclerotic and Hypertensive Heart Disease and Generalized Arteriosclerosis.—The annulus fibrosus was the common site of calcification on the mitral valve in patients with generalized arteriosclerosis and in those with arteriosclerotic and hypertensive heart disease (Table III). The 23 cases listed as arteriosclerotic and hypertensive heart disease are included in the group of 35 cases with generalized arteriosclerosis, except for 4 in which there was hypertensive heart disease but no arteriosclerosis. The average life span for these 2 groups was 69 and 70 years, respectively, and the average heart weight was 521 and 461 grams, respectively. These averages were essentially the same in those with aortic in addition to mitral valvular calcification, and were not significantly different in 24 patients without rheumatic heart disease or bacterial endocarditis who had neither generalized arteriosclerosis nor hypertension. Almost all patients with arteriosclerosis or arteriosclerotic and hypertensive heart disease were older than 50 years.

Primary Cause of Death.—The primary cause of death in 78 patients with mitral valve calcification was, in order of frequency: heart disease, carcinoma, and vascular disease, chiefly hypertension. Of the 37 cardiac deaths, one-third of the patients died of rheumatic heart disease, and almost as many died of myocardial infarction. One-fifth of the patients died of arteriosclerotic and hypertensive heart disease, and 4 died of bacterial endocarditis. In only seven of the 23 patients with arteriosclerotic and hypertensive heart disease was death due to the heart; in the remaining 16 cases of heart disease, the cardiac lesion was usually the cause of death. Congestive heart failure was diagnosed in five-sixths of the cases in which heart disease was a primary cause of death; murmurs were usually present in these cases. Angina pectoris was noted in approximately one-fourth of the cases.

The average heart weight is less in those with annulus than in those with leaflet calcification.

4. Mitral valve calcification does not give rise to symptoms or signs of heart disease. Its clinical importance lies in the fact that it is often an indication of the presence of significant cardiovascular disease.

5. Calcification of the mitral valve is always limited to the annulus fibrosus in hearts showing no cardiac lesion other than the valvular calcification.

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fibrosus.¹⁰ There is no evidence, from our study, that calcification of the mitral valve, regardless of its location, has an important bearing on clinical heart disease. This conclusion is evident from study of the whole group of 78 hearts with calcification of the mitral valve, but more particularly from study of the 15 hearts with calcification but without associated pathology. This statement applies to cardiac enlargement, murmurs, electrocardiographic abnormalities, heart failure, and cause of death.

Nevertheless, certain facts are of interest and importance. When mitral valve calcification is present, the incidence of associated cardiovascular disease is great; almost one-half of all the patients died of heart disease, usually rheumatic heart disease or myocardial infarction. In hearts showing no cardiac lesion other than valvular calcification, the latter was always limited to the annulus fibrosus. Leaflet calcification is usually regarded as evidence of mitral stenosis or rheumatic heart disease.^{10, 18} While this may be true insofar as the clinical demonstration of leaflet calcification is concerned, the more accurate post-mortem method used in this study indicates that only three-fourths of the cases with leaflet calcification had rheumatic heart disease, and that the latter was present in a few cases when calcification was limited to the annulus fibrosus. However, leaflet calcification in rheumatic heart disease indicates a more serious degree of heart involvement than is present when the annulus alone is calcified. These observations are in accord with Epstein's statement that patients with rheumatic heart disease who live past the age of 40 years develop calcium deposits similar in extent and distribution to those of patients with nonrheumatic heart disease¹¹ but that leaflet calcification indicates an advanced lesion.¹⁰ Others have reported mitral ring calcification in patients with rheumatic heart disease, the youngest of whom was 25 years old.^{4, 5} Two-thirds of the 78 hearts with mitral valve calcification had calcification in the coronary arteries; in most of these the valve calcification involved the annulus fibrosus. Epstein also found that disease of the coronary arteries and generalized arteriosclerosis in patients with mitral valve calcification was more frequent in those with nonrheumatic hearts.¹¹ The clinical application of these facts is impossible without an accurate differentiation between annulus and leaflet calcification.

CONCLUSIONS

1. A new and accurate method for detecting mitral valve calcification reveals that this condition is present in 10 per cent of unselected hearts. It occurs preponderantly in females.

2. Mitral valve calcification, especially of the annulus fibrosus, is in many cases not the result of an inflammatory process.

3. The annulus fibrosus is the most common site of calcification, and this type of deposit is usually found in the aged. The leaflets are involved much less commonly, and then largely in younger age groups; in these patients rheumatic heart disease is frequently present. Calcification may be confined to the annulus in rheumatic heart disease, but this type of deposit is found, as a rule, in a more advanced age group than that in which leaflet calcification is present.

bronchial mucosa, causing the accumulation of mucus and possibly of aspirated food particles in the respiratory tract; (d) paralysis of the bronchial musculature, causing narrowing or even collapse of the flaccid bronchioles during inspiration; and (e) loss of the Hering-Breuer reflex, causing an increase in the negativity of the intra-alveolar pressure as a result of the increased volume of inspired air. (2) *Pulmonary vessels*, resulting in (a) loss of vasoconstrictor tonus, causing dilatation of the pulmonary vessels; and (b) increased capillary permeability, causing transudation into the alveoli. (3) *Heart*, resulting in tachycardia and failure of the heart to adjust to circulatory changes. (4) *Gastrointestinal tract*, resulting in (a) faulty deglutition, and (b) regurgitation of food. Both (a) and (b) lead to the aspiration of food particles.

Most of these factors, singly or in combination, have been considered by previous investigators as the causes of the pulmonary changes following bilateral vagotomy.

Summarizing the conclusions given in the literature of the nineteenth century one may say that there were two main schools of thought. The first considered the pulmonary lesions, i.e., pulmonary edema and pulmonary consolidation, to be secondary to various disturbances of laryngeal, esophageal, or cardiac function, while the second regarded them as a primary disturbance of the function of the pulmonary vessels.

No attempt will be made to give a complete review of the literature on bilateral vagotomy. Only the works that appear to have some bearing on the pathogenesis of pulmonary edema will be reviewed.

The foremost representative of the school of thought which attributed the changes in the lungs to extrapulmonary causes was Traube,⁵ who published his first paper on bilateral vagotomy in 1846. He was, apparently, the most original of all his contemporaries, who to a great extent repeated his experiments with some variations.

Traube's most important contributions to the problem were the following: (1) Seven bilaterally vagotomized rabbits in whom tracheotomies had been performed lived for approximately twenty-four hours and showed either no or minimal pulmonary changes at autopsy. (2) In nine bilaterally vagotomized rabbits he tied the esophagus in the neck, cut it above the ligature and assured free drainage of mucus and saliva from the proximal end, thereby preventing the dripping of these substances into the lower airways. None of these animals showed pulmonary edema or consolidation when killed twenty-one to thirty-five hours post-operatively. (3) In four experiments he proved that squamous epithelium from the mouth or pharynx was present in the bronchi and alveoli of vagotomized rabbits killed several hours after the procedure. (4) He collected the secretions from the proximal end of the esophagi of vagotomized rabbits and injected them through a tracheotomy tube into the airways of two healthy rabbits. These died after eight and sixteen hours, respectively, and showed pulmonary edema and consolidation at autopsy. Traube concluded from (1) that the pulmonary changes were not due to the paralysis of pulmonary vagal fibers, from (2) that they were not due to the narrowing of the vocal cords following paralysis of the recurrent nerves, and from (3) and (4) that the pulmonary lesions were due to the failure of the vocal cords to close during deglutition in vagotomized animals, thus allowing mucus from the pharynx to get into the airways and cause aspiration pneumonia.

Traube's chief opponent was Schiff,⁶ who concluded that the lung changes were due to pulmonary vasomotor paralysis, for these main reasons: (1) In vagotomized and tracheotomized rabbits, guinea pigs, and dogs, he found pulmonary congestion, edema, and consolidation. He obtained this result at first with his own technique of using a quill or a thin glass tube for a tracheal cannula, but later he confirmed his own results, even when he used Traube's special cannula. This was a cannula into which the lower portion of the trachea was fitted. It also had a shield at its upper end to prevent the dripping of secretions into the bronchi. However, not all of Schiff's animals showed extensive pulmonary changes.

STUDIES ON THE PATHOGENESIS OF PULMONARY EDEMA FOLLOWING BILATERAL VAGOTOMY

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THE changes following bilateral cervical vagotomy have interested investigators for almost two thousand years. The procedure was apparently performed first by the Greek physician Rufus of Ephesus, who lived in the first century after Christ, and a few decades later by Galen. With the revival of science in the sixteenth century, interest in bilateral vagotomy was revived, and during the following centuries this procedure was performed by many experimenters, Valsalva¹ and Morgagni² being among the earlier ones. Valsalva was the first to describe pulmonary changes following bilateral vagotomy. These changes were then more thoroughly described by the French clinicians³ (Vieussens and Sénac), who called the process "inflammation." Since then the interest in this procedure has centered around the changes in the lungs. An important advance was made by Legallois,⁴ who was the first to consider laryngeal paralysis and paralysis of the pulmonary vagal fibers as possible pathogenetic factors responsible for pulmonary transudation and consolidation following bilateral vagotomy. The publication of Legallois' work was followed by a lively interest in bilateral vagotomy, which persisted for the greater part of the nineteenth century. The main problem of the studies was the pathogenesis of the pulmonary lesions. This interest stayed alive during the twentieth century and has even increased during the past few years.

Although some of the experiments of these investigators were done on dogs, cats, and guinea pigs, and more recently on rats, most of them were done on the rabbit, and the most important conclusions were drawn from work on this animal. Whenever more than one species of animals was used, the essential findings in the various species were similar in the hands of the same investigator, provided that animals of comparable age were used. Contradictory results, however, were often obtained by the various experimenters, which at times gave rise to sharp polemics, as between Traube and Schiff.

In reviewing the work of previous investigators it may be helpful to have clearly before our eyes the various structures, the functions of which might be disturbed by bilateral vagotomy.

On theoretical grounds the following possibilities emerge: (1) *Airways*, resulting in (a) inspiratory laryngospasm, causing a marked increase in the negativity of the intra-alveolar pressure; (b) inability of the vocal cords to close during deglutition, causing the aspiration of food particles into the airways; (c) loss of sensibility of the tracheal and

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balls in the bronchi. This procedure produced atelectasis, but not pulmonary edema or consolidation.

Claudio Bernard¹² came to the conclusion that the pulmonary lesions were produced by the change in the mechanics of respiration which follows bilateral vagotomy, i.e., by the infrequent respirations, with unusually large volumes of tidal air. Long before Bernard, the Englishman John Reid,¹³ and, later, Arnsperger¹⁴ and Boddaert,¹⁵ came to similar conclusions. They believed that the unusually deep and infrequent respirations of vagotomized animals caused stasis in the pulmonary capillaries and consequent transudation into the alveoli.

In summary, one may say that the investigators of the nineteenth century by their ingenious experiments greatly contributed to the elucidation of the factors causing the pulmonary changes in vagotomized animals. The fact that they did not distinguish clearly between pulmonary edema on the one hand and pneumonia on the other hand somewhat limits the value of their work from our viewpoint. However, the evidence presented by the bulk of the work, and particularly by the best-controlled experiments, those of Traube, Billroth, and Frey, suggests that all pulmonary changes which follow bilateral vagotomy may be due to a primary disturbance in laryngeal function.

The differentiation between pneumonia and pulmonary edema became distinct in the twentieth century. Kraus,¹⁶ and later Brunn,¹⁷ reported the production of pulmonary edema by the intravenous infusion of large amounts of normal saline into vagotomized animals. Kraus, working on rabbits and cats, thought that this type of pulmonary edema might be due to the loss of innervation of the pulmonary blood vessels. Brunn found that morphine, dial, paraldehyde, and extract from the posterior pituitary did not prevent pulmonary edema in vagotomized rabbits given large amounts of 1 per cent saline intravenously. He observed edema of the glottis in some of his animals and could indeed protect a number, but not all, of his rabbits by tracheotomy.

In recent years, the theory of pulmonary vasomotor paralysis has been supported by the work of Weiser and of Farber.

Weiser¹⁸ believed that vagotomy caused increased permeability of the pulmonary capillaries because in unilaterally vagotomized rats certain dyes (methylene blue, indigo carmine, etc.) introduced into the trachea after death diffused more readily from the lung which had been deprived of its vagal innervation than from the control lung. The amount of diffusion of the dyes was judged by the free eye. Colorimetric determinations were not made on account of small contaminations of the samples with blood.

Farber^{19, 20} has investigated the pathogenesis of pulmonary edema following bilateral cervical vagotomy in rabbits and guinea pigs. In rabbits¹⁹ he obtained results in agreement with those of Schiff and others, in that tracheotomized animals showed the same degree of pulmonary congestion and edema as nontracheotomized animals. The main difference was that no evidence of aspiration of food or of secretions from the mouth, nor of bronchopneumonia, was present in the rabbits. In vagotomized guinea pigs²⁰ under artificial respiration, he observed, after raising the sternum, that the heart beat regularly and vigorously until a few minutes before death, when dilatation of the right side became apparent. Autopsy revealed severe pulmonary edema and conges-

In some of his rabbits and dogs he found only a few small areas of consolidation; otherwise the lungs were normal. It is difficult to judge how often he found such small changes in his animals, as he very cautiously mentions them as: ". . . diese freilich exceptionellen, aber nicht so sehr seltenen Faelle. . ." (2) He found widespread pulmonary changes in animals with their esophagi tied and cut. (3) In rabbits he cut the gray portions of the vagal ganglia ("plexus ganglioformis"), leaving the white portions which carry the laryngeal fibers intact, and found the usual widespread pulmonary changes. Frey,¹⁰ however, repeated this experiment and found normal lungs in one rabbit, killed after twenty-two hours. In another, killed after twenty-six hours, very little pulmonary edema and one small area of consolidation were found. This investigator also quotes Friedlaender as having done this experiment on one rabbit, with negative results. (4) Cutting one vagus produces pulmonary changes. By anastomoses between the vagal fibers of the two lungs, or by a hypothetical pulmonary sympathetic innervation, Schiff tried to account for the fact that these changes were of slight degree. Frey, repeating these experiments, found no or minimal pulmonary changes if the rabbits were killed after a few days. If they were allowed to die spontaneously (survival time, two days to four weeks) they showed hyperemia of the lungs which was more marked on the vagotomized side.

Schiff's theory attracted few followers. We are aware of only two in the nineteenth century: Genzmer,⁷ whose conclusions entirely coincided with those of Schiff,⁶ and Wundt,⁸ who assumed that pulmonary vasomotor paralysis was one of the factors producing the changes in the respiratory tract of vagotomized animals.

Billroth⁹ using both Traube's and Schiff's methods of tracheotomy, found in his early experiments that the procedure in each case might or might not be followed by pulmonary changes. Later, however, with more careful technique, he never found lung lesions when he used Traube's methods. He also cut the vagi in two pigeons and one duck, because he could demonstrate that in birds only the lower portion of the larynx was supplied by the recurrent nerve. At death all birds showed perfectly normal respiratory tracts. He concluded that the pulmonary lesion following bilateral vagotomy was an aspiration pneumonia due to laryngeal paralysis.

Frey,¹⁰ in his monograph, thoroughly reviewed the literature on bilateral vagotomy and repeated most of the important experiments of previous investigators. His results were quite similar to those of Traube. Using the latter's tracheal cannula, he found pulmonary congestion in his vagotomized rabbits, but in only one a small amount of edema. In rabbits tracheotomized with Schiff's technique he reported marked pulmonary edema and congestion. He also showed that a tracheal cannula may produce pulmonary congestion in nonvagotomized rabbits, and in some of them may even produce edema. Furthermore, he confirmed Traube's findings that cutting of the recurrent nerves in the rabbit produced the same changes as vagotomy, only much more slowly. However, when, in addition to cutting the recurrent nerves the esophagus was tied, thereby favoring the flow of secretions into the trachea, the pulmonary changes appeared as rapidly as in vagotomized animals. Frey thus came to the same conclusions about the pathogenesis of the pulmonary lesions as Traube had.

The other investigators of this period concluded, as Traube had, that the pulmonary lesions were not due to paralysis of the pulmonary vasomotor fibers, but not all of them agreed with him as to the actual underlying cause of the lesions.

Mendelssohn,¹¹ prior to all these investigators, had come to the conclusion that the lesions in the respiratory tract of vagotomized animals were due to laryngeal paralysis. He advanced the interesting hypothesis that laryngeal paralysis resulted in deficient entrance of air into the lung and consequent suction on the blood vessel. "Sie (i.e., the air) verhält sich zur Schleimhaut der Lunge, wie die Luft unter einem trockenen Schröpfkopf (suction eup)."

All of Mendelssohn's contemporaries agreed that the narrowing of the vocal slit, particularly during inspiration, is not a factor in producing the changes in the lung. This belief was based on experiments of various investigators showing that after artificial constriction of the trachea by a band the lungs were found to be normal. In order to demonstrate that mucus in the bronchi did not create respiratory obstruction, Traube placed paper

(guinea pig and rabbit), unless laryngeal paralysis from the unilateral denervation produces respiratory obstruction (rat, guinea pig and rabbit).'' He concluded that pulmonary edema following bilateral vagotomy probably resulted from respiratory obstruction and that circulatory failure might also be a factor of some importance.

Very recently, Short²² has repeated the experiments on vagotomized rabbits with and without tracheotomy. Under the latter condition, he obtained severe pulmonary edema with regularity, while under the former, moderate pulmonary edema occurred in only three of twelve rabbits. He also showed that a tracheal cannula may produce severe pulmonary edema in nonvagotomized rabbits. Short thought that the appearance of the lungs at autopsy was strongly suggestive of asphyxia, and therefore he concluded that this was the major factor causing the pulmonary changes. In tracheotomized animals he attributed the asphyxia to the presence of mucus plugs. The theory that slow asphyxia was responsible for the pulmonary lesions in vagotomized animals had been first advanced by Schafer.²³

The interest in bilateral vagotomy has been stimulated in recent years mainly by the occurrence of pulmonary edema in patients with lesions of the central nervous system. Farber's work has been regarded by Luisada²⁴ as contributing to the evidence that pulmonary edema may be produced by nervous factors. The present study was undertaken mainly to test the validity of this conclusion.

BILATERAL CERVICAL VAGOTOMY AND SYMPATHOTOMY IN THE RAT UNDER ETHER ANESTHESIA

Methods.—Twenty-five young adult rats of piebald strain (*Mus norvegicus*), weighing 150 to 250 grams, were used. Under ether anesthesia the vagus nerve was resected low in the neck. In eight of the 25 rats the sympathetic chains were also cut low in the neck. The clinical course of the animals was observed, with frequent notations of the character of the respirations. If the rats survived, they were also watched at intervals during the first and second nights.

Laryngoscopy was performed in most animals immediately following vagotomy, and in a few cases later during the course. Laryngoscopy was carried out by using as the source of light an ophthalmoscope from which the head piece carrying the lenses had been removed. With the anesthetized animal tied down on its back, the tongue was seized with a blunt forceps and pulled upward. When the light was placed near the posterior portion of the palate, the larynx and the movements of the vocal cords were clearly seen. If death was not observed, the survival time was set arbitrarily at the midpoint between the time the animal had last been seen alive and the time when it was found dead. Complete autopsy was carried out at once if the death of the animal was observed. In some rats, however, post-mortem examination was not performed until one to two hours after death, and occasionally not until several hours thereafter in animals which survived for a long time. The right lung was immediately immersed in 10 per cent formalin. The left lung was placed, without loss of blood or edema fluid, into a weighing bottle. After weighing on an analytic scale, this lung was dried

tion. From the fact that the heart action appeared undisturbed on inspection, he concluded that there were no important alterations in the heart which might have caused the pulmonary edema following bilateral vagotomy. In the same paper he reported a series of experiments in which pieces of cotton saturated with 1 per cent novocain solution were placed anteriorly and posteriorly over the lung hila of nonvagotomized guinea pigs under artificial respiration. Severe pulmonary edema and congestion developed just as in vagotomized animals. The type of respiration preceding the onset of pulmonary edema was not described. In a later communication Farber²⁰ reported the intravenous infusion of large amounts of normal saline, ranging from 135 to 350 c.c., into 20 vagotomized rabbits within ten to fifteen minutes. Ten of these animals were tracheotomized and ten were not. Some of the rabbits died spontaneously soon after the infusion was stopped. The others were killed fifteen minutes afterward. All showed marked pulmonary edema and congestion. There were no important differences noted at autopsy between animals with and those without tracheotomy tubes. The same results were obtained if vagotomy was preceded by a large saline infusion and followed by a small one. Infusion of similar amounts of saline into healthy rabbits produced moderate pulmonary congestion but no edema. The clinical course of these rabbits was characterized by rapid shallow breathing, interrupted only rarely by very short attacks of "respiratory distress" accompanied by generalized convulsions. The vagotomized animals, breathing slowly and deeply, showed similar but more frequent crises, usually commencing one to two minutes after the infusion had been started. Farber was unable to produce pulmonary edema in atropinized rabbits to whom similar amounts of physiologic solution of sodium chloride were given intravenously. He concluded from his first two studies that "neuropathic pulmonary edema," as he termed it, following bilateral vagotomy, was caused by "disturbance to or abolition of the pulmonary vasomotor nerves." In his third paper he suggested that alterations in the pulmonary vessels secondary to loss of vagal innervations were of primary importance in the production of this type of pulmonary edema, but that other processes also were responsible. His evidence suggested to him that pulmonary edema in patients suffering from central nervous system disorders with involvement of the brain stem were caused by disturbances, either central or peripheral, in the vasomotor control of the pulmonary vessels.

Lorber,²¹ in contradistinction to the last-named investigators, came to the conclusion that pulmonary edema in vagotomized animals was caused by extrapulmonary causes. He reported that vagotomized rats die within two hours and that the lungs of these animals show extensive pulmonary congestion and edema. He thus confirmed the report of Weiser, whose rats died in three to six hours. Tracheotomy considerably prolonged the life of vagotomized rats, the lungs exhibiting only minimal changes. Lorber thought that "the common denominator in all cases in which pulmonary congestion and edema were seen in any degree was respiratory obstruction." Intrathoracic vagotomy below the recurrent laryngeal nerve on one side, and cervical vagotomy on the other side, performed ten to fourteen days later, permits "almost indefinite survival

At times thin serous fluid was found in the airways. The lungs were usually dark red in color and rather voluminous; if the edema was less marked, they were medium red or mottled and their volume was only slightly increased. In pharynx, larynx, and trachea we observed variable amounts of viscid mucus.

Group With Long Survival Time: The second group (seven rats) also had repeated attacks of inspiratory obstruction, but after these ceased (usually after several hours) the animals breathed quietly, inspiration being only slightly or not at all labored. A slight inspiratory noise was present at times, but periods of inspiratory crowing were observed only rarely. The survival time of these animals ranged from twenty-five to eighty-eight hours. The later course of these rats was characterized by slowly increasing drowsiness and weakness. If aroused, however, the animals were very irritable; if taken out of the cage, they usually developed a transient inspiratory crow. From the mouth and nostrils there often dripped a considerable amount of foul-smelling mucus, which the animals could be observed to chew and swallow. The respiratory rate increased somewhat in the later stages; the rate usually ranged between 40 and 60 per minute. In the rare cases in which these animals were observed at death, the respirations were seen to become more and more shallow and finally to stop. Only one rat, which survived twenty-five hours, was observed to die with signs of inspiratory distress. We have never observed a vagotomized rat to consume solid food. The amount of water they drink is very small.

At autopsy these rats showed either no pulmonary edema or pulmonary edema of such slight degree that it could not be considered as even a major contributing cause of death. The lungs were normal or slightly increased in size, their color was medium to dark red, often mottled, and they showed varying degrees of bronchopneumonia and at times also patchy atelectasis. In this group large amounts of mucus also were found in the airways. The liver showed a moderate degree of congestion at times. No other significant changes were found in either group. The upper row in Table II illustrates the fact that the longer was the survival time of the animals, the lesser was the degree of pulmonary edema.

The water content of the left lung as determined by the dry weight almost invariably paralleled the degree of edema found on gross examination. Occasional disagreement between the two observations might be due to uneven distribution of pulmonary edema in the two lungs, a condition which was observed at times on gross examination of the lungs, or to the presence of interstitial edema not detected on gross examination. The average dry weight of the left lung in the group with pulmonary edema of moderate or marked degree was

TABLE II. RELATION OF SURVIVAL TIME TO DEGREE OF PULMONARY EDEMA (VAGOTOMY UNDER ETHER AND UNDER URETHANE ANESTHESIA)

	DEGREE OF PULMONARY EDEMA			
	MARKED	MODERATE	SLIGHT OR MINIMAL	NONE
Ether anesthesia				
Average survival time in hours	8.5	9.5	22.5	51.5
Urethane anesthesia				
Average survival time in hours	19		70	

by exposure to a temperature of 100 to 110° C. until a constant weight was obtained. The water content of the lung was thus determined. In all rats in this series the division or the integrity of the sympathetic chains was checked by dissection under the dissecting microscope.

Results.—Immediately after cutting the second of the vagi the respirations became slow and deep. The respiratory rate varied from 16 to 30 per minute in the great majority of cases, but in a few rats it was as high as 40 per minute. In many animals, but not in all, a marked inspiratory crow appeared immediately or approximately one minute after bilateral vagotomy. Whenever this was present inspirations were quite labored, all auxiliary respiratory muscles being used vigorously. Laryngoscopy of these animals revealed the vocal cords immobile and rather near to the midline but leaving a fair-sized slit open for the passage of air during most of the respiratory cycle. During the second half of inspiration, however, the vocal cords were drawn closely together; the air forced through this narrow pathway produced the respiratory crow.

It is of considerable importance that we observed several rats which did not develop this inspiratory crow but did have labored inspirations immediately after vagotomy. If these animals were not much disturbed by laryngoscopy and did not develop an inspiratory stridor during the procedure, they did not show the inspiratory spasm of the vocal cords.

There was no important difference in the clinical course or survival time, or in the incidence of pulmonary edema between the 17 animals which had only the vagi cut, and the eight which had the sympathetics in addition to the vagi cut (Table I). Hence, the 25 rats will be discussed together. Twenty of these 25 rats could be placed into two groups, which differed in their survival time, clinical course, and also in the pulmonary findings at post-mortem examination.

TABLE I. COMPARISON OF THE EFFECT OF BILATERAL VAGOTOMY AND SYMPATHOTOMY UNDER ETHER ANESTHESIA

	NUMBER OF ANIMALS	SURVIVAL TIME IN HOURS			PULMONARY EDEMA*	
		MINI- MUM	MAX- IMUM	AVERAGE	NO.	%
Bilateral vagotomy	17	3½	72	19	11	65
Bilateral vagotomy and bilateral sympathotomy	8	2½	88	22	4	50

*Pulmonary edema of moderate or marked degree.

Group With Short Survival Time: The animals in the first group (13 rats) had either continuous or frequently recurrent inspiratory obstruction, to which they succumbed at various intervals ranging from forty-five minutes to fourteen hours. In this group death occurred under extreme inspiratory distress, the rat leaping wildly through the cage in vain attempts at inspiration.

At autopsy these animals showed pulmonary edema of moderate or marked degree. Whitish froth was seen on the cut surface of the right lung and in the bronchi, and in the more severe cases also in the trachea. It also appeared at the hilus of the left lung, which was dropped uncut into a weighing bottle.

low figure in view of the fact that an incidence of 100 per cent has been reported in vagotomized rats. To investigate the possibility that the use of either anesthesia might have influenced our results, the following group of rats was operated upon under a different anesthetic.

BILATERAL CERVICAL VAGOTOMY UNDER URETHANE ANESTHESIA

The methods employed in this series of experiments were the same as in the previous one, except that urethane was used as the only anesthetic and the sympathetics were not cut. Urethane was chosen on account of its negligible effect on circulation and respiration. It was administered to 12 rats by intraperitoneal injection, in amounts varying from 700 to 1,300 mg. per kilogram of body weight. The animals which had received the smaller doses were usually well awake several hours postoperatively. The few rats requiring the larger doses often remained under rather deep anesthesia for longer periods, at times for twenty-four to thirty-six hours.

In this series, in contrast to the previous one, audible and visible inspiratory laryngeal obstruction was rare. Laryngoscopy revealed a vocal slit which was fairly narrow during inspiration and expiration, but only very rarely was there an inspiratory laryngospasm. Nevertheless, inspiration was often, but not always, rather labored immediately after vagotomy. This usually subsided after a variable time, but periods of moderately labored inspiration often reappeared during the later course. The survival time in this group was considerably longer than that in the rats operated upon under ether anesthesia; the average time for the entire group was approximately fifty-three hours, with a range from approximately four and one-half to one hundred six hours.

The autopsy findings differed in two important respects from those of the previous series. First, the incidence of pulmonary edema of moderate or marked degree was considerably lower; and second, the incidence and the extent of bronchopneumonia was much increased, as was also the amount of mucus in the airways. Only four rats of the 12 showed pulmonary edema of a significant degree, while the others had either no or minimal to slight pulmonary edema. Of the four animals exhibiting moderate or marked edema, one had continuous inspiratory laryngeal obstruction for its entire survival time of four and one-half hours, and one suddenly developed severe inspiratory obstruction, leading to death in a few minutes. The other two animals, like most rats in the entire group, had episodes of moderately labored inspiration; they were not observed at death. Again in this series the survival time of the rats developing pulmonary edema of significant degree was much shorter than that of the animals without or with little pulmonary edema (Table II).

The dry weight of the left lung was determined in the majority of the animals in this group. Again there was a close correlation between the amount of pulmonary edema observed on gross examination and the moisture content of the lung.*

This series of rats again showed the importance of respiratory obstruction in the development of pulmonary edema. The following group of experiments was done in an attempt to avoid inspiratory obstruction.

*For this reason the dry weight determination of the lung tissue was omitted in the remaining series of experiments.

14.8 per cent; the individual values ranged from 10.5 per cent to 17.5 per cent, except for one instance in which it was 19.7 per cent. In the group without pulmonary edema or with pulmonary edema of slight degree, the average dry weight was 22.9 per cent; the individual values ranged from 22.1 per cent to 26.2 per cent, with one exception of 18.7 per cent.



Fig. 1.—Section through lung showing dilatation of the capillaries, and pinkish staining material in some of the alveoli and around the small vein in the left upper corner. In this area there is also extravasation of red blood cells.

The microscopic findings in the lungs usually confirmed the observations made on gross examination, the only exception being our inability to demonstrate small and sometimes even moderate amounts of pulmonary edema under the microscope. The fixation of edema fluid in slices of rats' lungs, which by necessity are thin, was not appreciably improved by dropping the tissue into warmed formalin. In the majority of cases, however, pinkish staining fluid with entrapped air bubbles was seen in the alveoli. The same material was often seen to accumulate around small pulmonary blood vessels, apparently distending the perivascular lymphatics (Fig. 1). At times small areas of emphysema, undetected on gross examination, were seen.

The five rats not included in the previous account because they did not show a similar correlation between survival time and autopsy findings, died after 28, 28½, 12, 10, and 6 hours, respectively. The first two, which were not observed at death, showed moderate and marked pulmonary edema, respectively, but the latter three showed no or minimal edema.

The incidence of pulmonary edema of moderate or marked degree in the entire group of twenty-five rats was 60 per cent (15 rats), which is a surprisingly

vagotomy, and possibly not even that in the tracheotomized animal, as we shall point out later.

In recent years the statement has been made that inspiratory obstruction alone may produce pulmonary edema. There is, however, little experimental evidence reported in detail to substantiate this statement. Warren, Peterson, and Drinker²⁵ demonstrated markedly increased lymph flow from the lungs in dogs breathing against inspiratory resistance. Moore and Binger²⁶ found pulmonary edema in only one of six dogs breathing against inspiratory resistance. The other animals showed mild to moderate pulmonary congestion, which usually was more marked over the lower portions of the lungs. Barach²⁷ reported that "edema of the lungs may occur in three hours, with circulatory failure, after continuous breathing through a resistance." In another paper²⁸ he mentions that dogs inspiring against a negative pressure of 4 cm. of water for six hours show a progressive rise in the intrapleural negative pressure and that at autopsy severe pulmonary congestion and edema of the hilus and basal regions, with emphysema at the periphery, were found.

The following experiments were carried out to determine whether well-marked pulmonary edema could be produced with regularity by causing rats to breathe against inspiratory resistance and whether expiratory resistance in addition would change the incidence of pulmonary edema.

RATS BREATHING AGAINST INSPIRATORY RESISTANCE

Methods.—Rats of the same strain and of approximately the same weight as those in the previous series were used. Under intraperitoneal urethane anesthesia a Y-shaped tracheal cannula of thin metal was inserted. Each of its arms was connected by rubber tubing to a somewhat modified Marriotte tube (Fig. 2). As illustrated, the tubes offer no resistance to inspiration or expiration. By immersing the glass tube touching the water surface in *A* more or less deeply into the water, any desired degree of inspiratory resistance can be produced. Similarly various degrees of expiratory resistance are produced by lowering the corresponding glass tube in *B*. After insertion of the tracheal cannula, no inspiratory resistance was introduced for fifteen to forty-five minutes. This was a control period to demonstrate proper operation of the cannula without obstruction. Then inspiratory resistance, usually measuring 4 to 5 cm. of water, but at times measuring up to 8.5 cm. of water, was produced, according to what resistance the particular animal could overcome. If the resistance was too high, no air bubbles were sucked through the water in tube *A*, and consequently rebreathing and marked anoxemia would have occurred had the resistance not been reduced. During the later course a reduction of the inspiratory resistance to 2.5 cm., or even to zero, was necessary for short periods of time to prevent asphyxia and premature death of the animals. The rats were observed very closely and changes in respiration were noted. Complete autopsy was performed either immediately after or shortly after death. A few representative lung specimens were examined microscopically.

Results.—In a few preliminary experiments, the animals survived only two to three hours. At autopsy they showed considerable congestion of the lungs,

RIGHT THORACIC AND LEFT CERVICAL VAGOTOMY

To rule out the factor of laryngospasm, the right thoracic vagus was cut below the origin of the recurrent nerve in a group of six rats, while the left vagus was cut low in the neck immediately afterward. This type of operation, first performed by Genzmer,⁷ has recently been performed by Lorber,²¹ who, however, cut the left cervical vagus ten to fourteen days after the right thoracic vagus was cut.

Under ether anesthesia, the right sternoclavicular joint was severed and the clavicle reflected laterally, as described by Lorber.²¹ The medial portion of the first rib was resected and the second rib was retracted downward. Care was taken not to handle the vagus above the origin of the recurrent laryngeal nerve, below which the vagus was then cut. Left cervical vagotomy followed immediately afterward. The integrity of the right recurrent laryngeal nerve was checked by laryngoscopy, which revealed the left vocal cord immobile near the midline, while the right showed the normal vigorous excursions with respiration. At autopsy the right recurrent laryngeal branch was found intact in all cases.

Immediately after, or very shortly after vagotomy, respirations became slow and deep, inspiration being moderately labored in spite of the absence of laryngospasm. This type of respiration continued for some time, usually not more than twelve hours, and then gave way to somewhat faster, less deep, and little or not at all labored breathing. Periods of moderately labored inspiration recurred later during the course; these could be eased temporarily by wiping thick mucus out of the hypopharynx. As to their general behavior, these rats were quite similar to those with bilateral cervical vagotomy. The average survival time in this group was sixty-six hours, varying in individual rats from thirty to one hundred twenty hours. At post-mortem examination pulmonary edema of moderate or marked degree was found in three rats; two rats showed no pulmonary edema and one showed very slight pulmonary edema. The lungs of all animals were moderately congested and showed varying degrees of bronchopneumonia.

As has been demonstrated, inspiratory obstruction was not avoided by the operative procedure described. Therefore, at least in the rat, thoracic vagotomy is not a suitable procedure for ruling out the obstructive factor associated with bilateral vagotomy.

The question arises, of course, whether respiratory obstruction, and particularly inspiratory obstruction, can actually produce pulmonary edema. The investigators of the nineteenth century, with the exception of Mendelssohn,¹¹ denied this. They based their conclusion on experiments in which respiratory obstruction was produced by narrowing the trachea with a constricting band or by letting the animal breathe through a very narrow cannula. These procedures failed to produce pulmonary edema or consolidation. Traube⁸ also obstructed bronchi by paper balls, and consequently found atelectasis but not the pulmonary changes produced by vagotomy. It should be noted that all these procedures gave rise to inspiratory and expiratory obstruction. They, therefore, do not simulate the condition present in the nontracheotomized animal with bilateral

could be prolonged for periods up to one-half hour. Some animals died during a brief absence of the observer from the laboratory. At autopsy all 10 animals showed pulmonary congestion and pulmonary edema of moderate to marked degree. Peculiarly, edema was always, and congestion was at times, more marked in the left lung than in the right. The color of the lungs of the various rats varied from light red to rather dark red. Pulmonary edema was not necessarily more marked in the dark red than in the light red lung. In the latter there always was one dark red area in the hilar region of the left lung. The rat which survived for only one and one-half hours had the least pulmonary edema. In the other animals, however, the degree of pulmonary edema was not always proportionate to the length of survival. The pulmonary edema seen so readily on gross examination of the lungs could not be seen microscopically in all cases in which sections were obtained. We encountered here the same difficulty in fixing the intra-alveolar transudate as we did in the vagotomized animals. Dilatation of the capillaries was always present and often marked. In addition, small areas of emphysema were noted.

RATS BREATHING AGAINST INSPIRATORY AND EXPIRATORY RESISTANCE

The same methods were used as in the previous experiments except that expiratory resistance was added to the inspiratory resistance. In four rats the expiratory resistance was approximately one-half the inspiratory, while in the other animals it was of equal magnitude.

Results.—In this group the respiratory rate was always reduced, usually by one-fourth to one-third of the initial rate, but in a few animals only by 8 to 12 respirations per minute. This is in agreement with the finding of previous investigators that expiratory resistance diminishes the respiratory rate. Respirations in this series were deeper and more visibly labored than those in the rats breathing against inspiratory obstruction only. One animal in this group survived for approximately one and one-half hours; the survival times of the others ranged from approximately two and one-half to seven hours, the average for the entire group being approximately four hours. Death occurred in a manner similar to that of the preceding series. At autopsy two of the 13 rats in this group showed pulmonary edema of moderate, and two of minimal degree. In the other animals only slight pulmonary congestion was present.

The experiments in the last two groups of rats show that pulmonary edema may be produced with regularity if the animals breathe against inspiratory resistance only.

Farber²⁰ has raised the important objection that pulmonary edema following vagotomy and intravenous infusions of large amounts of normal saline, could not be attributed to inspiratory obstruction, as the edema occurred too rapidly to be due to this factor. To investigate the validity of this objection the following experiments were performed.

RAPID INTRAVENOUS INFUSION OF NORMAL SALINE IN VAGOTOMIZED RATS WITH TRACHEOTOMY AND IN RATS BREATHING AGAINST INSPIRATORY RESISTANCE

Methods.—Rats similar in weight to those in the previous series were used. Under intraperitoneal urethane anesthesia a tracheotomy was performed and

but no pulmonary edema. Consequently, an effort was made to keep the rats alive for longer periods of time. Of 10 consecutive animals, nine lived from approximately three to six hours under inspiratory resistance varying between the limits outlined previously. One animal survived for only one and one-half hours. The average survival time of the ten rats was approximately four hours. The character of the respiration under inspiratory resistance was as follows: The respiratory rate was essentially unchanged, increasing or decreasing not more than 10 to 15 respirations per minute from an initial rate of 100 to 140. This is in accordance with the findings of Anrep and Samaan.²⁹ Moore and Binger²⁶ found that dogs under sodium barbital anesthesia, when made to

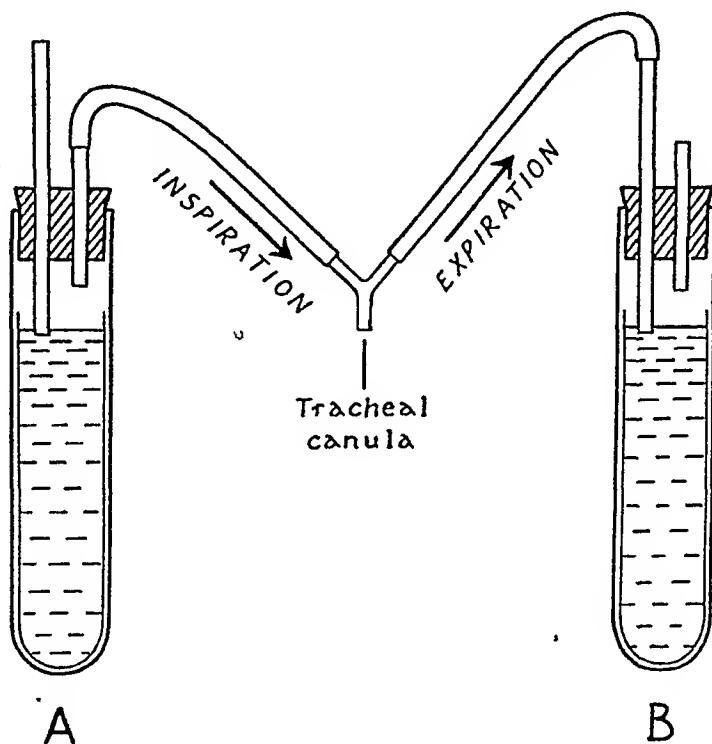


Fig. 2.—Explanation in text.

breathe against inspiratory resistance, developed a considerable increase in the respiratory rate. In our animals, when the resistance was too high to be overcome by the inspiratory effort, a definite slowing of the respirations was noted. The depth of the respirations in our rats was affected only a little by inspiratory resistance, but a slight increase in the depth could usually be detected. Slight to moderate inspiratory retraction of the costal margins was always present. There was slight dilatation of the alae nasi, but none of the other auxiliary respiratory muscles were used. This type of breathing remained unchanged until the terminal period, the onset of which occurred from one-half hour to a few minutes before death. At that time the animal gradually became unable to overcome the inspiratory resistance. Respirations became slow and shallow, rebreathing began, and respirations ceased within one to two minutes, unless the resistance was lowered at once. In some animals, if the resistance was lowered temporarily, to be raised again after a few minutes, life

after ending the infusion. At autopsy the amount of pulmonary edema was definitely less than that found in the first group. There was never any frothy fluid in bronchi or trachea. The amount of pulmonary edema on the cut surface of the left lung was slight in all cases; in the right lung the edema was slight in four cases, and of moderate degree in two. Pulmonary congestion was slight in four rats and of moderate degree in the remaining two.

The group of six rats breathing against inspiratory resistance and receiving intravenous saline showed respirations very similar to those described above in rats breathing against inspiratory resistance only. Respirations became slow and labored only immediately before death. Until then they continued at a normal rate and were not at all or only slightly labored. Death occurred spontaneously in five animals in periods of from twenty-three to forty-two minutes. The sixth animal was killed by intravenous sodium cyanide thirty-eight minutes after the infusion had been started. The amount of saline injected ranged from 45 to 60 cubic centimeters. At autopsy two rats had marked pulmonary edema extending up into the trachea, three had pulmonary edema of moderate degree and one, of slight degree. The lungs of all showed moderate or marked pulmonary congestion.

PLASMA AND BLOOD VOLUME DETERMINATION IN BILATERALLY VAGOTOMIZED RATS

In an additional group of rats we tried to determine the mode of death of those animals which survived bilateral vagotomy for a considerable time. In this group plasma and blood volume determinations were made in order to investigate the possibility that peripheral circulatory collapse developed in these animals.

Methods.—In healthy rats, weighing from 160 to 240 grams, blood volume determinations were carried out by the method of Gibson and Evans³⁰ and Gibson and Evelyn³¹ as modified by Beckwith and Chanutin³² for the rat, with only minor modifications adopted by Williams and Barnum.³³ The first blood sample was obtained from the rat's tail ten minutes after injection into the exposed external jugular vein of an accurately measured amount (200 to 300 mg. in various rats) of a 1 per cent solution of T-1824 from a calibrated tuberculin syringe. Four or five additional blood samples were taken subsequently at five-minute intervals. The plasma samples were diluted 60 times with normal saline. The micro attachment of an Evelyn photocolormeter* was used for the colorimetric readings. Normal saline, rather than diluted plasma, was used as the standard solution, as it has been shown that it gives the same colorimetric reading as highly diluted plasma.

The blood volume determinations were done under urethane anesthesia, supplemented by small amounts of ether when necessary. One rat, BV1, had 1 mg. of sodium pentothal, intraperitoneally, in addition. Immediately after the last blood sample had been taken, bilateral vagotomy was performed. In all but one of the animals the nerve was cut in the cervical region. Rat VTH7 alone was

*The author expresses his thanks to Dr. Maxwell Little of the Department of Physiology and Pharmacology of the Bowman Gray Medical School for helpful advice in setting up this method and for the loan of the Evelyn photocolormeter.

the Y-shaped tracheal cannula connected with the Marriotté tubes in a group of six rats. No respiratory resistance was produced, the glass tubes just touching the water surface. The cervical vagi were cut and immediately afterward the infusion of an 0.85 per cent solution of sodium chloride was started. The solution was administered by drip from a graduate cylinder which was kept at a constant height in all experiments. The cylinder was connected to a glass adapter connected to a 24-gauge hypodermic needle by means of rubber tubing. In all experiments the needle was inserted into the right external jugular vein just above the clavicle, the tip of the needle pointing toward the rat's head. The rate of infusion, varying approximately from 1.5 to 2 c.c. per minute, was kept fairly constant throughout these experiments. There was one exception, in which a smaller quantity of fluid was given. Animals which did not die spontaneously were killed by the intravenous injection of a 0.05 per cent solution of sodium cyanide: respirations stopped after a few seconds, and were usually accompanied by several convulsive movements.

The procedure in the second group of six rats was identical except that no tracheotomy was performed.

In a third group of six tracheotomized but not vagotomized rats, inspiratory resistance of 4 to 7 cm. of water was produced, and then the intravenous infusion was started at a rate similar to that of the previous group.

Results.—In the animals in which vagotomy was performed, respirations became very slow and deep immediately following this procedure. At the same time the prolonged inspiration became somewhat labored, while the relatively short expiration remained perfectly easy. Usually the labored inspiration was accompanied by a moderate increase in the rise of water in the expiratory tube (Fig. 2), thus indicating an increase in the negativity of the intrathoracic pressure. Very soon, as the intravenous infusion was running in, inspirations became more labored, and in some animals continued unchanged until death, while in others they gradually became even more labored. The respiratory rate in some rats either remained essentially unchanged or showed a moderate increase during the later course. In five of the six vagotomized rats 50 to 65 c.c. of saline were given over a period of twenty-seven to forty minutes. These animals were killed by intravenous injection of sodium cyanide a few minutes after ending the infusion. The sixth rat died spontaneously after twenty-four minutes when 22 c.c. of saline had been infused. In this animal and in one other, a very marked degree of pulmonary edema extending up into the trachea was found. The other rats showed pulmonary edema of moderate degree, except for one in which only a small amount of pulmonary edema was present.

*The lungs of all were moderately or markedly congested.

None of the animals in the second group (vagotomized, but not tracheotomized) showed evidence of laryngospasm. Consequently, inspiration was only slightly labored in the beginning of the experiment, and remained so in some instances up to the end, while in others it became moderately labored during the later course. In this group the amount of intravenous saline and the time in which it was administered were quite similar to those conditions in the tracheotomized group. All rats in the second group were killed a few minutes

volume determination. In these animals there was a rather close agreement of the blood and plasma volume changes, with one exception (Rat BV19), in which the decrease in plasma volume was 11 per cent greater than the decrease in blood volume. The average decrease in plasma volume was 10.6 per cent for the entire group. In only four of the 10 rats was there a reduction of the plasma volume of more than 15 per cent.

Thus, in the majority of our rats peripheral circulatory failure did not appear to be an important factor. We believe that, in the rats not dying of pulmonary edema, bronchopneumonia and inanition were the major causes of death. Our study does not rule out, of course, the possibility of peripheral circulatory collapse later in the course, particularly shortly preceding death.

Plasma and blood volume determinations on five vagotomized rabbits were performed by Farber.²⁰ In two, an insignificant increase and decrease, respectively, of the plasma volume were present, while the decreases in the other three animals ranged from 17.6 to 30.7 per cent. The blood volumes of the rabbits were more uniformly decreased, but some of his animals had suffered considerable hemorrhage from the trachea. The main difference in the arrangement of his study and ours was that his animals showed clinical evidence of pulmonary edema when the plasma volume determination was performed. The results obtained, however, are not strikingly different. The fact that he obtained significant reductions of the plasma volume in a higher percentage of his animals cannot be evaluated on account of the small number of animals used.

In eight of our rats, which appeared in good enough condition following the second blood volume determination, the mean arterial blood pressure was measured by cannulation of the aorta with a mercury manometer. The readings ranged from 100 to 140 mm. Hg in various animals, thus indicating a normal or slightly elevated arterial pressure.

The heart rate before and after vagotomy was determined in this series by taking electrocardiograms. The heart rate before vagotomy varied from 315 to 500 per minute in various animals. A few minutes after vagotomy it was usually found to be elevated by 100 to 250 beats, but occasionally only by 50 beats, per minute.

The animals surviving the second blood volume determination were killed by withdrawing the cannula from the aorta, which caused death in fifteen to thirty seconds. The two rats in which aortic cannulation was not performed were killed by decapitation. In none of these ten animals was there any pulmonary edema. On the other hand the rats dying spontaneously or during the second blood volume determination showed moderate or marked pulmonary edema in approximately half the cases.

DISCUSSION

Until recently the rat had been used only sporadically as the experimental animal for investigations concerning the effects of bilateral vagotomy. In recent years, however, two important studies have appeared in which the rat was used exclusively (Weiser¹⁸) or predominantly (Lorber²¹). These two investigators came to totally different conclusions about the pathogenesis of pulmonary edema

subjected to a right-sided thoracic vagotomy. It proved very difficult to determine the right moment for the second blood volume determination, as the time of death of vagotomized rats cannot be predicted with any accuracy. Thus many animals died either before or during the second blood volume determination. Out of a group of approximately 22 rats, the second blood volume determination was successfully completed in only 10. It was carried out in these animals twenty-two to twenty-four hours after vagotomy. At this determination, blood was obtained before injection of the dye and the plasma sample, diluted 60 times, served as the standard for the colorimetric readings. The clinical course of the rats in this group was quite similar to that in the urethane series described previously, the only difference being the shorter period of anesthesia, since smaller amounts of urethane (approximately 700 mg. per kilogram of body weight) were given.

TABLE III. BLOOD AND PLASMA VOLUMES BEFORE AND AFTER BILATERAL VAGOTOMY

RAT	PLASMA VOLUME*		CHANGE† %	BLOOD VOLUME*		CHANGE† %	REMARKS
	BEFORE	AFTER		BEFORE	AFTER		
VTH7	3.7	2.7	-27.0	7.1	5.0	-29.6	Only animal with thoracic vagotomy
BV1	3.4	3.6	+ 5.8	7.3	6.8	- 5.9	
BV6	4.8	4.1	-14.6	7.5	6.6	-12.0	
BV7	3.8	3.7	- 2.6	7.4	6.1	-17.6	
BV10	4.1	3.3	-19.5	7.8	6.1	-21.8	Animals transfused
BV11	4.4	3.4	-22.7	7.9	6.0	-24.0	
BV13	3.4	3.7	+ 8.8	-	-	-	
BV19	4.4	3.6	-18.2	8.3	7.7	- 7.2	
BV20	4.7	4.1	-12.6	8.5	8.0	- 5.9	
BV21	3.3	3.2	- 3.1	6.7	6.2	- 7.5	
Total average	4.0	3.5	10.6	7.6	6.5	14.6	

*In cubic centimeter per 100 grams of body weight.

†Values obtained on the basis of preoperative body weight.

Results.—The values for plasma and blood volumes in ten rats before and after bilateral vagotomy are charted in Table III. The plasma volumes of our normal rats ranged from 3.3 to 4.8 c.c. per 100 grams of body weight, with an average of 4 cubic centimeters. The corresponding values for blood volume varied from 6.7 to 8.5 c.c. with an average of 7.6. Following vagotomy the plasma volume was slightly increased in two rats and was decreased in eight. In these eight the amount of decrease ranged from 2.6 to 27 per cent. The greatest decrease (27 per cent) occurred in the animal in which the right thoracic vagus had been cut and which, therefore, had been exposed to much greater operative trauma than the other animals. The change in blood volume did not always run parallel to the change in plasma volume. Of the first four rats in the series one (Rat BV1) showed a decrease of 5.9 per cent in the blood volume, while the plasma volume was increased by 5.9 per cent; and another (Rat BV7) had a decrease of 17.6 per cent in the blood volume, while the plasma volume was decreased by only 2.6 per cent. This discrepancy was attributed to the removal of approximately 1 c.c. of blood during the first blood volume determination. In the remaining six animals in the series, the amount of blood removed was replaced by an equal amount of citrated rat blood immediately after the first blood

indicated by small areas of emphysema which were noted on microscopic examination.)

The importance of inspiratory obstruction as the primary factor causing pulmonary edema in vagotomized rats is emphasized by the following points: (1) Bilateral vagotomy in the rat under ether anesthesia does not necessarily produce pulmonary edema. (2) Rats surviving the period in which inspiratory obstruction is marked rarely show pulmonary edema. (3) Urethane anesthesia decreases laryngospasm and further decreases the incidence of pulmonary edema. (4) All rats showing pulmonary edema of significant degree had either marked continuous or marked intermittent labored inspiration for a variable period before death.

Our studies do not support the conclusion of previous investigators (Schiff, Farber) that pulmonary vasodilatation and increased capillary permeability of neuromuscular origin are important factors in the production of pulmonary edema of this type. Further important proof that pulmonary vascular changes are, at the most, of secondary importance comes from the fact that some of the previous workers (Traube, Frey) regularly prevented the production of significant pulmonary changes by tracheotomizing their animals before vagotomy. Billroth, and even Schiff at times, obtained similar results in some of their animals. Lorber observed that in his tracheotomized vagotomized rats pulmonary edema was produced only if respiratory obstruction occurred through the accumulation of mucus in the tracheal cannula or in the airways. It is true that a few workers found pulmonary edema and congestion even in tracheotomized animals. But the fact that this occurred in the hands of some investigators, while not in the hands of others, seems to indicate that the difference in the results was due to a difference in technique.

The theory that pulmonary vasodilatation is directly due to vagotomy (i.e., to denervation of the pulmonary vessels) also rests on insecure ground, because the importance of pulmonary vasomotor fibers in regulating the blood flow through the lungs is still controversial. While some investigators believe that vasomotor fibers play an important part in this regulation, others deny this. For a discussion of this subject the reader is referred to the writings of Daly,³⁶ Wiggers,³⁷ and Hamilton.^{38a} The most recent work, that of Hamilton and his co-workers,^{38b} who used intact unanesthetized animals and differential manometers, is probably the most convincing investigation of the pressure relationships in the pulmonary circulation up to date. From this work Hamilton reached the conclusion, first expressed by Dixon and Hoyle,³⁹ that "the vasomotor activity of the pulmonary arterioles is a feeble vestigial mechanism, which is without important function."

The theory of Traube and his school, namely that the inability of the vocal cords to close during deglutition is responsible for the pulmonary changes following bilateral vagotomy, can be accepted only to explain bronchopneumonic lesions, and possibly pulmonary edema of late onset, which is perhaps of inflammatory origin. Early pulmonary edema, particularly that following vagotomy plus intravenous infusion of saline, cannot be explained on this basis.

following bilateral vagotomy, but agreed in an important finding, namely that all vagotomized rats died within a few hours, autopsy revealing moderate to severe pulmonary edema in all cases. In contrast, many of our rats lived for a considerably longer period, some of them up to three or four days. Moreover, only two-thirds of our animals operated upon under ether anesthesia and only one-third of those operated upon under urethane developed pulmonary edema of moderate or marked degree.

This important discrepancy between our findings and those reported by previous investigators is not due to accidental cutting of the cervical sympathetic chains in addition to the vagal nerves, as rats in which the vagi only and others in which sympathetics and vagi were cut showed similar survival times and a similar incidence of pulmonary edema.* We believe the reason for the discrepancy to be the lesser degree of laryngospasm and, therefore, of inspiratory obstruction in our rats.

That the larger experimental animals, apparently with the exception of the rabbit, may survive bilateral vagotomy practically indefinitely has been shown repeatedly. Schafer²³ demonstrated that bilaterally vagotomized cats could be kept alive for many months if the vocal cords had been cauterized. That dogs can survive in the absence of vagal innervation of the lungs and heart was demonstrated by Boothby and Shamoff,²⁴ who divided all vagal branches between the recurrent laryngeal nerve and the gastrointestinal branches. Pavlov²⁵ also reported survival of dogs if one vagus was cut below the recurrent laryngeal nerve and the other in the neck.

Laryngospasm, however, is not the only cause of inspiratory obstruction in vagotomized rats. In rather deeply anesthetized animals laryngospasm may never occur. Furthermore, a few hours after vagotomy the vocal cords assume the cadaveric position, and remain in this position unless the animal is disturbed. Nevertheless, in these groups of animals severe inspiratory obstruction may occur. Undoubtedly, in most instances, this is due to accumulation of mucus in the airways; it can at times be alleviated by wiping out mucus from the hypopharynx. When this is not possible, the point of obstruction may be lower down in the respiratory tract. Mucus was apparently an important factor causing inspiratory obstruction in those rats which had one cervical and one thoracic vagus cut. In spite of the fact that laryngospasm was ruled out in these animals, some of them still showed severe inspiratory distress.

It may be asked why the accumulation of mucus should give rise to obstruction which is predominantly inspiratory. We believe this may be due to the movement of mucus plugs from channels of wider diameter to channels of smaller diameter during the inspiratory effort. Thus, an amount of mucus incapable of creating obstruction higher up will produce obstruction at a point lower in the airways. During the expiratory effort the plug will move in the opposite direction and therefore will be much less likely to produce respiratory obstruction. (That localized expiratory obstruction may nevertheless occur may be

*Cutting of the cervical sympathetics, which probably leaves most pulmonary sympathetic fibers intact, does not, of course, disprove the possibility that thoracic sympathetic denervation might influence the pulmonary changes following bilateral vagotomy.

remained virtually unchanged in these experiments. All these animals developed pulmonary edema. If, however, expiratory resistance also was introduced, there developed a considerable increase in positive expiratory pressure as shown by high rises of water in the inspiratory tube. In most of these animals, consequently, pulmonary edema did not develop.

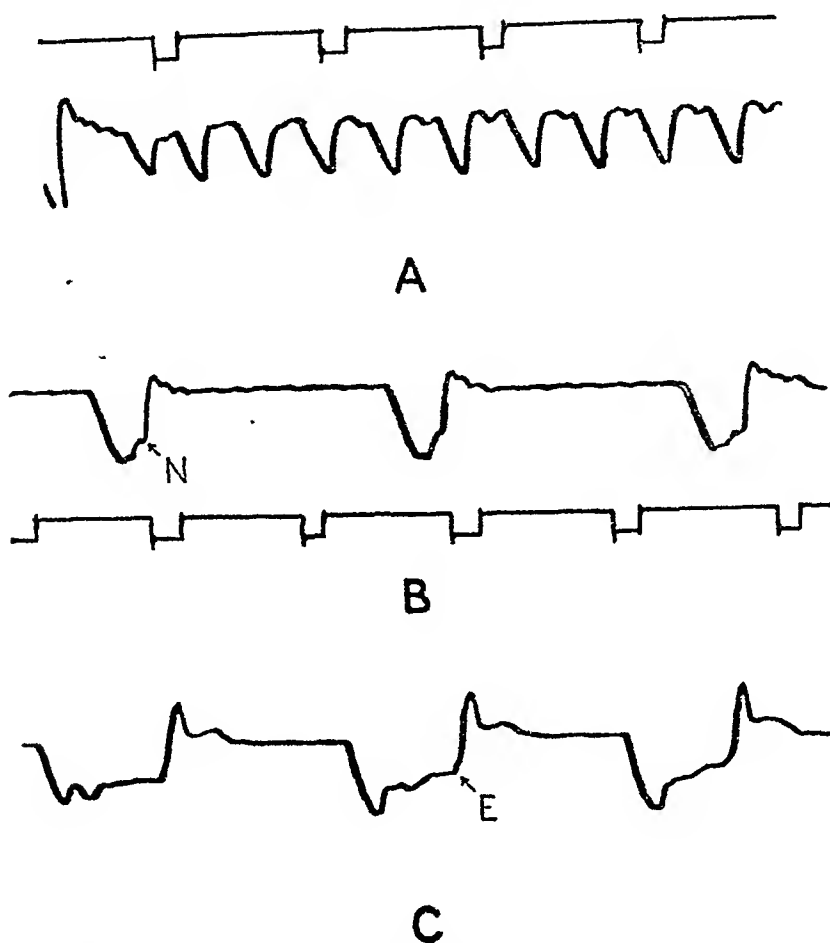


Fig. 3.—*A*, Respiratory tracing before vagotomy (inspiration = downstroke, expiration = upstroke). *B*, Immediately following vagotomy. That inspiration continues up to notch *N* is shown in *C*, in which air withdrawn was pushed back at *E*. Time tracing in seconds.

Similar observations were made in tracheotomized vagotomized animals. In these there was always a higher rise of the water during inspiration than during expiration. The difference was not as striking as in the rats breathing against inspiratory resistance. Usually a difference of 2 to 3 cm. was observed, but occasionally it was as much as 5 to 6 centimeters. This finding strongly suggests that, following vagotomy, there was an increase in the negativity of the intra-alveolar pressure during inspiration.

The objection might be raised that in vagotomized animals with a tracheal cannula there could not have been inspiratory obstruction, since laryngospasm was ruled out in such experiments. We observed, however, that inspiration in these animals was moderately labored and prolonged immediately after vagotomy, that is, at a time when pulmonary congestion and edema, or the accumulation of mucus, could not have been responsible for this type of respiration. We also observed that labored and prolonged inspiration with laryngospasm developed in

It also appears doubtful that slow asphyxia, as such, may produce pulmonary edema. This theory was first postulated by Schafer²³ and recently was restated by Short²² to explain the pulmonary lesions in bilaterally vagotomized animals. According to Drinker's studies,⁴⁰ a very marked degree of anoxia has to be present before increased pulmonary transudation, as evidenced by an increase in pulmonary lymph flow, appears. This increase did not take place until the oxygen content of the inspired air was lowered to 8.5 per cent. Drinker thought that even this increase in lymph flow originated only from those areas of the lung which were poorly or not at all aerated on account of the use of artificial respiration. This relative immunity of the lung capillaries to lack of oxygen can probably be explained on the basis that they may derive their oxygen supply not only from the blood but from the alveolar oxygen as well. That severe anoxia exists in vagotomized animals has never been shown. It is unlikely to be a causative factor in the production of pulmonary edema in the short experiments that employ vagotomy plus the intravenous administration of fluids. It may be an additional factor in vagotomized animals with relatively long survival times, but we do not believe that it is of primary importance.

It appears from our studies that a close correlation exists between the occurrence of inspiratory obstruction and the development of pulmonary edema in vagotomized animals. This causal relationship was first suggested by Mendelssohn.¹¹ Recently Lorber²¹ concluded that respiratory obstruction was the most important factor producing pulmonary edema in vagotomized animals.

Our experiments have shown that pulmonary edema of moderate to marked degree can actually be produced with regularity by inspiration against resistance. In rats breathing against inspiratory resistance, or in rats with inspiratory obstruction, a markedly negative intra-alveolar pressure must be present during the forced inspiratory effort. This abnormal negative pressure will tend to overcome the osmotic pressure in the pulmonary capillaries and draw a transudate into the alveoli.

We did not attempt to measure the intrapulmonary pressure in our animals and were unable to measure intrapleural pressure in rats without producing pneumothorax of considerable degree. That the intra-alveolar pressure was highly negative in animals breathing against inspiratory resistance was indicated by the following observations. Under ordinary respiration the water in tubes A and B (Fig. 2) was sucked up into the glass tubes touching the water surface during inspiration in B and during expiration in A. A and B thus acted alternatively as water manometers, giving a rough measurement of the pressure in the other tube and in the respiratory tract. Under normal respiration, with the tubes just touching the water surface, the water rose in them approximately 3 to 4 cm., thus indicating a negative pressure in the respiratory tract during inspiration and a positive pressure during expiration. When inspiratory resistance was produced, the water in the expiratory tube rose to approximately 9 to 12 cm. during inspiration, thus indicating a considerable increase in the negativity of the intrapulmonary pressure. The pressure during expiration

will favor the transudation of fluid into the alveoli. It is clear, however, that these conditions do not necessarily lead to pulmonary edema. In our rats, as we have mentioned before, inspiration often ceased to be labored and prolonged at varying intervals following vagotomy. It was in these animals that pulmonary edema was not found at autopsy.

The phenomenon of labored and prolonged inspiration immediately following vagotomy might be explained by two possible mechanisms: One possibility is that the very slow and deep inspiration of vagotomized animals, which is due to the loss of the Hering-Breuer reflex, as such, induces a marked increase in the negativity of the intra-alveolar pressure on account of the increased inspiratory volume of air. The second possibility, first suggested by Auer and Gates,⁴¹ was that the bronchioles of vagotomized animals may become narrowed during inspiration due to the flabbiness of the bronchial musculature, which has been deprived of its nervous innervation. This phenomenon could, of course, occur only in bronchioles (as they contain no cartilage in their walls) and not in the bronchi. The dilatation of the bronchioles in vagotomized rabbits was clearly demonstrated in Short's microscopic studies.²² That under abnormal conditions the bronchial lumen may become narrowed during inspiration has been observed by Amberson⁴² through the bronchoscope in a patient with chronic nontuberculous fibrosis, emphysema, and pulmonary infection, and in two patients with pulmonary tuberculosis. As Amberson had no direct evidence concerning the underlying pathologic lesion, he assumed that the phenomenon was due to atrophy or malacia of the cartilages.

Either of the two mechanisms, but particularly the latter one, would increase the negativity of the intra-alveolar pressure during inspiration. Thus the same basic mechanism would operate in vagotomized rats, in which laryngospasm is either spontaneously absent or artificially obviated by tracheotomy, as would operate in vagotomized rats with laryngospasm. That there are also other factors favoring the occurrence of pulmonary edema during forced breathing, besides an intra-alveolar pressure of abnormal negativity, is indicated by the work of Hamilton^{38a} on anesthetized dogs breathing stertorously. Recording differential pressures between pulmonary artery and vein, as well as between pulmonary artery and thorax, they noticed the gradient of pressure to fall almost to zero during inspiration. During expiration the pressure gradient, before returning to normal, rises to two or three times its normal value.

In addition, Huggett⁴³ showed long ago that inspiratory resistance increases the cardiac output. Recently Shuler and his associates⁴⁴ have demonstrated an increase of the output of the right ventricle and a decrease of the output of the left ventricle during inspiration. These changes they attributed to the aspiration of blood into the right ventricle and to an increase in the pulmonary vascular capacity. These workers also showed that these circulatory conditions were reversed during expiration. In breathing against inspiratory resistance, however, and particularly during the slow, labored inspiration of vagotomized animals, the circulatory changes during inspiration must far outweigh those occurring during the unhampered expiration. It is clear that the abnormal circulatory dynamics accompanying labored inspiration will pro-

rats with the right thoracic and the left cervical vagus cut,* apparently before the accumulation of mucus could take place.

We tried to obtain additional objective evidence to substantiate the observation that inspiration appeared prolonged and labored even in tracheotomized rats with bilateral vagotomy, and that it occurred immediately following vagotomy, before mucus could accumulate in the airways. In three rats, breathing through a Y-shaped tracheal cannula connected to Marriotte tubes, respirations were recorded before and immediately after bilateral vagotomy, on a kymograph from a small tambour, which was connected by a T tube into one of the circuits. Satisfactory records were thus obtained (Fig. 3). The relative duration of inspiration and expiration is very distinct before, but not after, vagotomy. As the volume of respiration increases, overshooting occurs in the tambour during inspiration. That inspiration actually lasts up to the end of the notch *N* (Fig. 3, *B*) was proved by connecting a syringe instead of a rat to the system. When 0.5 c.c. of air was quickly injected, the same overshooting occurred as did the vagotomized rats, the lever then remaining at a lower level until the plunger of the syringe was pulled back (Fig. 3, *C*). The absolute and relative durations of inspiration and expiration in two rats, before and after bilateral vagotomy, are seen in Table IV. In a third rat we obtained similar results, which are not reported in detail since no time tracing was taken. These experiments demonstrated that vagotomy approximately doubled the duration of a single inspiration, while it did not change a single expiration. On account of the slow respiration following vagotomy, the total duration of inspiration was reduced, but the duration of expiration per minute was much more reduced. The increase in the ratio inspiration to expiration, following vagotomy, would probably have been even more striking had not the system through which the rat was breathing in itself offered some resistance to inspiration. The presence of such resistance was indicated by the relative prolongation of inspiration even before vagotomy.

Consequently, we may say that immediately following vagotomy inspiration becomes prolonged and labored, that it is accompanied by an abnormal increase in the negativity of the intra-alveolar pressure, and that this is not counteracted by a prolonged expiration or an increase in the positive pressure during expiration. Again we want to emphasize that these pressure relationships

TABLE IV. DURATION OF INSPIRATION AND EXPIRATION BEFORE AND AFTER BILATERAL VAGOTOMY

		INSPIRATION*		EXPIRATION*		QUOTIENT INSPIRATION EXPIRATION
		SINGLE	PER MINUTE	SINGLE	PER MINUTE	
Rat K2	Before vagotomy	0.21	22.05	0.11	11.55	1.9
	After vagotomy	0.41	13.94	0.10	3.40	4.1
Rat K3	Before	0.17	23.80	0.11	15.40	1.5
	After	0.34	10.88	0.11	3.54	3.1

*Duration in seconds.

*The question whether the labored inspiration was due to a laryngeal reflex was answered by doing a complete laryngectomy in three tracheotomized, vagotomized rats. The clinical course, particularly the type of respiration and the pathologic findings in these animals, which also received intravenous saline, was quite similar to those with intact larynx.

for pulmonary edema in such instances. The author has not observed clinically patients with cerebral lesions who develop pulmonary edema, and is therefore unable to say whether inspiratory obstruction occurs late during their course. The importance of preventing inspiratory obstruction in patients under general anesthesia is obvious.

SUMMARY

The pathogenesis of pulmonary edema observed in patients with lesions of the central nervous system in the absence of heart disease has never been satisfactorily explained. Some investigators believe that similar conditions exist in experimental pulmonary edema following bilateral vagotomy. They attribute this type of pulmonary edema to disturbances in the vasomotor control of the lung vessels and believe that the same factor is operating in the "neurogenic" pulmonary edema in man. Our studies on bilateral vagotomy in the rat do not support these conclusions. The evidence obtained by our work suggests that the important factor in pulmonary edema following bilateral vagotomy is inspiratory obstruction. We do not deny the possibility that "neuropathic" pulmonary edema may occur in man. However, bilateral vagotomy does not appear to furnish proof for the existence of pulmonary edema of such pathogenesis.

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duce stagnation of abnormally large amounts of blood in the pulmonary vascular bed. This in turn will favor the transudation of fluid into the alveoli if a great negative intra-alveolar pressure is present at the same time.

Our further experiments showed that pulmonary edema can be produced with regularity, and in a short time, in rats breathing against inspiratory resistance while receiving normal saline intravenously at a rapid rate. The degree of pulmonary edema and the rapidity with which it occurred in these animals and in vagotomized and tracheotomized animals receiving intravenous fluids was quite comparable. Thus Farber's contention²⁰ that inspiratory obstruction could not have been a factor causing pulmonary edema in the short-term experiment of vagotomy plus the infusion of intravenous saline, was not sustained.

There was, however, a striking difference in the degree of pulmonary edema between the two groups of rats mentioned previously and the group of vagotomized but not tracheotomized rats. Inspiration was more labored in the animals with, than in those without, tracheotomy, which we attribute to the fact that the tracheal cannula and the system of Marriotte tubes in itself presented some resistance to inspiration, as we have pointed out previously. The degree of pulmonary edema in the nontracheotomized rats receiving intravenous fluids was small indeed. This again emphasizes the importance of inspiratory obstruction or resistance in the genesis of this type of pulmonary edema. It also stresses the role played by the tracheal cannula in producing pulmonary edema, as pointed out recently by Short,²² and long ago by Traube, who devised a special cannula to prevent a harmful effect on the respiratory tract.

It appears that the occurrence of pulmonary edema in vagotomized animals can be best accounted for by the marked disturbances of respiration, particularly by inspiratory obstruction, which follow bilateral vagotomy. We believe, therefore, that the conclusions that have been drawn from this experimental procedure regarding the pathogenesis of pulmonary edema in patients with lesions of the central nervous system are not justified. From our studies we cannot, of course, deny that a true "neuropathic" pulmonary edema, that is, pulmonary edema due to pulmonary vasodilatation and increased capillary permeability, may exist in man. But we believe that the procedure of bilateral vagotomy furnishes no experimental proof for the existence of pulmonary edema of such pathogenesis. We, furthermore, doubt that a procedure like bilateral vagotomy, which causes such complex and hardly controllable physiologic disturbances, can be a suitable one to either definitely prove or disprove the existence of a truly neuropathic pulmonary edema.

It would seem that pulmonary edema as seen in patients may at times be due to inspiratory obstruction. Pulmonary edema of moderate degree and without demonstrable cause is often found at autopsy. This induced Cohnheim to say that many people do not die because they have pulmonary edema, but they have pulmonary edema because they die. He thought that the edema in these cases might be caused by the right ventricle continuing to work after the left has stopped. The question arises whether inspiratory obstruction caused by the accumulation of mucus, and possibly by the relaxed tongue, may be responsible

THE PERIPHERAL BLOOD FLOW AND RECTAL AND SKIN TEMPERATURES IN HYPERTENSION

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THE subject of hypertension has engaged the attention of many investigators in recent years. Stimulus was given to these investigations by the experiments of Goldblatt and his associates relating to the rise in blood pressure which follows the preparation of an ischemic kidney^{1, 2} and by the studies of Page^{3, 4} relating to the chemical background of hypertension. The surgical treatment of hypertension, which has also increased the interest in and study of this subject, will be discussed in a succeeding paper.⁵

From an anatomic study of renal biopsies from one hundred hypertensive patients, Castleman and Smithwick⁶ concluded that "the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing the hypertension. Furthermore these observations are not in keeping with the concept that renal ischemia due to pre-existing renal vascular disease is the cause of essential hypertension in man." Talbott, Castleman, Smithwick, Melville, and Pecora,⁷ from a correlation of renal biopsies with renal clearance, concluded that constriction of efferent glomerular arterioles was not present in the early stage of renal vascular disease.

Pickering⁸ found the rate of blood flow through the forearm in hypertensive subjects the same as that in subjects with normal blood pressure and concluded that, owing to vasoconstriction, the resistance offered by the vessels of the forearm is increased in hypertension. Prinzmetal and Wilson⁹ also found that the resting blood flow in the arm was within normal limits and concluded that increased vascular resistance is not confined to the splanchnic area but is generalized throughout the systemic circulation. Abramson and Pierst,¹⁰ using the venous occlusion plethysmographic method, found that the resting blood flow through the arm and leg was significantly greater, but that through the hand was less in hypertensive subjects than in normal subjects. They concluded that their observations directly contradicted the prevailing theory that there is generalized and uniformly increased peripheral resistance in hypertension.

One of the results of these studies has been the accumulation of a vast amount of literature which has contributed much to the understanding of hypertension. However, the mechanism of hypertension, whether it is of nervous or humoral origin, still remains unexplained. It appeared to us that a study of the total peripheral blood flow in essential hypertension might be of interest in

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with 73 c.c. per square meter per minute for a group of normal young male subjects¹⁸ at the same room temperature (Table I, Fig. 1). While the peripheral blood flow is statistically significant in the group of normal young adults, the fluctuations in the hypertensive groups are such that the difference from the young normal male group is not significant. There was no significant difference in the peripheral blood flow in the men of the hypertensive group as compared

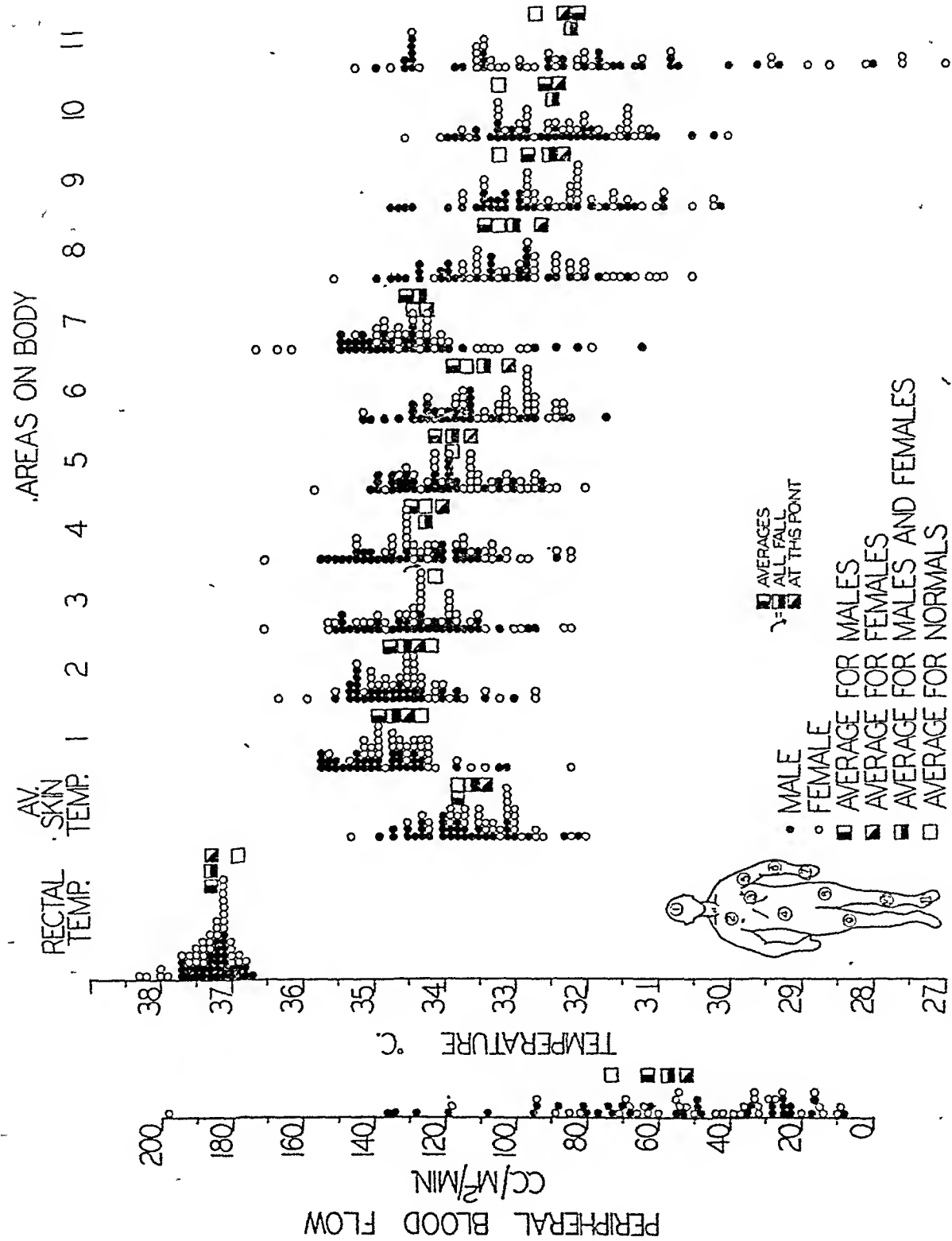


Fig. 1.—In this figure are shown the peripheral blood flows and rectal and skin temperatures of patients suffering from hypertension. Each open (female) and closed (male) circle represents the average of the morning's observations on one patient (Table I). The averages for all the men, all the women, and of both are shown by appropriate symbols. The average for normal men¹⁸ is shown for comparison. The figure also serves as a series of frequency diagrams.

the whole general problem as there are conflicting views about the blood flow in local areas. We have accordingly measured the amount of blood allotted to the peripheral circulation in patients suffering from essential hypertension. These observations form the basis of this report. In another paper the effects on the peripheral blood flow of splanchnic resection for the lowering of blood pressure will be appraised.⁵

Sixty-nine observations were made on 56 patients who had arterial hypertension; 25 were men, and 31 were women. The ages ranged from 19 to 66 years.

METHODS

The peripheral blood flow was measured by our modification^{11, 12} of the method of Hardy and Soderstrom.¹³ Hardy and Soderstrom have shown that, at a temperature below 28° C., the skin functions like a dead insulator when the subject is lying nude in the basal state, and that blood flow to the skin, thermal conductivity of the peripheral tissues, and vaporization are constant and minimum. With an increase in blood flow to the periphery, more heat is brought from the deeper tissue to the surface. This increases the thermal conductance of the superficial tissues; therefore, changes in thermal conductance become an index of peripheral blood flow. With this method, blood flow is expressed as a function of heat loss, surface area, *average weighted skin temperature*, and rectal temperature. The method requires the recording of skin and rectal temperature¹³ at known intervals, oxygen consumption,¹⁴ height, and body weight.^{15, 16} The skin temperatures were recorded with a Hardy-Soderstrom radiometer¹³ from eleven points on the anterior surface of the body as shown in Fig. 1. With this method the amount of blood allocated to the whole periphery of the body is measured, rather than the flow in local areas, and may be expressed in cubic centimeters per square meter of body surface per minute.

Plan of Procedure.—The plan of procedure was that described in recent publications.^{12, 17} All measurements were carried out in the morning before breakfast with the patients in a basal metabolic state. They were brought to the constant temperature room and allowed to lie in bed nude, covered only with a sheet. One hour was allowed for adjustment to the room temperature of 27° C. and 50 per cent humidity. Measurements of skin and rectal temperatures were made at twenty-minute intervals. Each set of observations covered a period of sixty to one hundred minutes. Blood pressure and pulse rate were recorded between temperature readings. The basal metabolic rate was measured at the beginning and again at the end of the morning's observations.

Four to six sets of skin and rectal temperatures were recorded from which three to five estimations of peripheral blood flow could be made for the morning. The data recorded in Table I for each date show the averages of the peripheral blood flows, temperatures, blood pressures, and heart rates for the morning.

OBSERVATIONS

The results of the observations are shown in Table I and Fig. 1.

Peripheral Blood Flow.—The average peripheral blood flow of the whole group was 57 c.c. per square meter of body surface per minute, as compared

H. S. 372225 M. 32	12/17/43	8	37.02	33.70	35.0	34.5	33.2	33.6	34.0	33.3	34.9	32.8	32.9	33.5	33.8	158/108	66	- 8	Hypertension. Enlarged heart
J. O'K. 231295 M. 40	3/10/43 3/20/43	77 23	37.68 37.44	34.28 34.36	35.5 35.5	35.2 35.2	35.4 35.5	35.3 35.4	34.7 34.7	34.4 34.6	35.1 35.4	34.3 34.3	33.1 33.1	32.4 32.0	32.0 32.3	181/126 181/117	88 75	+19 -12	Hypertension
C. W. 331023 M. 48	7/ 2/42	80	37.24	33.55	34.3	34.8	34.1	34.8	34.6	34.0	31.2	33.3	32.5	31.8	30.0	186/116	85	+ 5	Hypertension
H. V. 281681 M. 40	10/20/42	49	37.59	33.96	34.9	34.6	35.1	34.9	34.4	33.9	34.2	34.7	32.8	32.8	30.8	173/136	82	+22	Hypertension. Enlarged heart
H. O. 381111 M. 44	4/11/44	25	37.34	32.06	33.1	33.0	32.7	32.4	32.6	31.7	32.1	31.4	31.5	31.0	31.2	186/126	63	+ 5	Hypertension. Slightly. Enlarged heart. Hypertensive encephalopathy
N. C. M. 36	5/ 6/44	34	36.08	33.65	34.3	34.5	33.5	34.2	33.0	32.8	34.4	33.5	33.4	33.1	32.9	132/86	66	-11	Hypertension
A. R. 249201 M. 40	4/23/40 5/ 1/40	73 74	37.11 36.92	33.49 33.77	35.1 34.7	34.6 34.3	34.6 33.6	34.5 34.0	34.5 33.9	34.1 33.7	34.4 34.5	33.3 33.3	33.4 33.9	31.9 33.1	29.6 33.4	187/124 127/96	69 68	-11 -11	Hypertension. Enlarged heart
W. M. 224740 M. 26	2/ 6/39 2/ 8/39	94 134	37.28 37.25	34.68 34.66	35.7 35.6	35.3 35.2	35.4 35.3	35.7 35.5	34.9 35.0	35.1 35.0	35.1 35.3	34.3 34.5	34.6 34.5	33.5 33.3	31.8 32.5	201/139 196/135		+22 +10	Malignant hypertension
A. B. 256256 M. 19, 21, 23 resp't.	2/14/40 3/25/42 6/16/44	128 49 88	37.24 37.12 36.99	34.25 33.81 34.24	35.1 34.5 34.6	35.3 35.0 35.2	35.4 35.2 34.3	35.6 35.1 35.2	34.7 34.1 33.9	34.2 33.6 33.6	34.0 33.7 34.8	34.9 33.9 34.0	33.4 33.1 32.9	33.8 32.8 33.2	30.8 29.3 34.9	173/124 196/127 205/141	68 59 73	- 4 - 6 +11	Hypertensive cardiovascular case. Malignant hypertension Encephalopathy
F. B. 316266 M. 37	1/ 8/42	53	37.23	33.44	34.6	34.7	34.3	34.1	34.5	33.9	34.4	32.8	31.4	32.0	31.8	181/130	86	+ 5	Hypertension. Arteriolari sclerosis. Cardiac insufficiency Chronic passive congestion liver, spleen, and lungs
P. L. 319076 M. 24	3/ 1/42	16	37.20	33.07	34.6	34.0	33.5	34.0	32.6	34.7	34.8	32.5	31.9	32.4	30.8	168/121	67	-22	Hypertensive cardiovascular case
T. G. 311596 M. 13	1/ 5/42	119	37.07	34.47	35.2	34.9	34.9	35.0	34.1	34.3	35.2	33.8	33.7	33.9	34.4	146/116	92	- 9	Hypertension

TABLE I. OBSERVATIONS RELATING TO THE PERIPHERAL BLOOD FLOW IN PATIENTS SUFFERING FROM HYPERTENSION

CASE, HISTORY NO., SEX, AGE (YR.)	DATE	PERIPHERAL BLOOD FLOW (C.C./ M.2/ MIN.)	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHTED SKIN TEMPERATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1	2	3	4	5	6	7	8	9	10	11				
<i>Data Relating to Twenty-Five Male Subjects</i>																			
G. W. 385137 M. 42	6/17/44	55	37.33	33.77	35.7	35.2	34.1	33.8	34.9	33.7	35.4	32.8	33.3	31.7	32.3	205/122	80	+12	Hypertension. Slightly enlarged heart
G. W. 386933 M. 48	6/19/44	28	37.67	33.06	34.7	34.1	34.0	33.8	33.8	33.6	33.9	32.4	30.9	31.1	31.6	251/162	98	+34	Hypertension. Enlarged heart Aortic insufficiency. Myocardial infarct. Arteriolosclerosis
C. C. 386438 M. 40	6/3 /44	48	37.06	33.90	35.2	34.9	34.2	33.7	34.2	34.4	35.0	32.8	32.9	32.6	34.4	218/139	89	+5	Essential hypertension. Enlarged heart
R. R. ' 388459 M. 47	6/23/44	35	37.73	33.91	35.7	35.5	34.9	34.5	34.6	34.1	35.3	32.8	32.7	32.2	31.3	217/131	80	+13	Hypertension
R. B. 301492 M. 25	7/18/41	95	37.51	34.03	34.4	34.6	34.5	34.7	33.9	33.8	34.9	33.9	33.2	33.0	33.4	170/106	72	+11	Hypertension
B. O'B. 292901 M. 22	4/ 5/41	23	37.21	33.26	35.2	34.0	34.6	34.5	34.1	33.8	34.7	32.9	31.3	31.9	28.0	128/98	69	- 4	Hypertensive cardiovascular case
D. S. 339187 M. 47	10/ 9/42	68	37.62	33.09	34.4	33.8	33.9	34.1	33.2	32.9	32.4	33.3	32.1	32.3	30.7	211/128	73	± 0	Hypertension
E. S. 268711 M. 41	6/22/40 6/24/40	17 28	37.51 37.15	32.83 32.98	33.8 33.2	34.4 33.8	33.9 33.8	34.0 33.7	33.2 33.0	33.3 32.3	34.5 34.4	32.2 31.8	30.9 31.7	30.5 31.4	31.8 34.5	190/139 164/119	94 84	+20 +13	Hypertension. Probable coronary occlusion

M.D. 384959 F. 46	5/29/44	63	37.06	33.49	34.5	34.4	34.3	34.5	33.6	33.1	34.7	32.2	32.1	32.2	33.4	172/110	69	± 0	Hypertension. Arteriolar nephrosclerosis
S.C. 384676 F. 33	5/27/44	32	37.22	33.11	34.3	33.7	33.6	33.1	33.5	32.7	34.4	32.4	32.2	32.1	33.2	150/107	73	- 4	Essential hypertension. Enlarged heart
C.N. 386907 F. 42	5/31/44	71	37.38	33.92	35.1	35.0	34.9	33.4	34.1	33.7	35.4	33.1	33.4	31.9	32.9	140/85	66	+ 1	Essential hypertension. Enlarged heart
A.A. 318945 F. 41	2/27/42	39	37.35	33.54	34.4	34.8	34.5	34.7	32.9	33.7	34.8	33.5	32.1	31.6	32.0	208/116	73	- 10	Hypertension. Bronchial asthma Enlarged heart
M.J. 315435 F. 43	1/ 3/44	82	37.53	34.51	35.1	35.1	35.1	35.2	34.6	34.2	35.2	34.1	33.7	33.6	33.7	241/126	65	- 2	Hypertension. Hypertensive encephalopathy. Enlarged heart
I.H. 287756 F. 26	4/11/44	33	37.47	32.01	32.2	32.7	32.3	32.4	32.4	32.4	32.9	31.6	31.2	31.2	31.2	221/148	85	+ 30	Hypertension
B.G. 311888 F. 25	11/10/41	33	37.64	32.71	35.0	34.9	34.8	34.2	33.6	32.8	33.3	31.3	30.5	30.0	29.4	177/116	92	+ 14	Essential hypertension. Enlarged heart
C.O. 311597 F. 44	1/ 5/42	32	37.08	33.26	34.5	34.5	35.6	34.1	33.1	33.4	34.4	32.7	32.4	32.0	27.6	169/117	79	- 4	Essential hypertension
O.K. 368408 F. 38	1/12/44	60	37.92	33.85	35.0	34.6	35.0	34.4	34.1	33.2	34.1	33.2	32.8	33.2	31.7	209/132	78	- 5	Essential hypertension
C.D. 372511 F. 25	12/ 7/43	42	38.20	34.25	35.1	35.9	35.5	35.2	34.5	33.2	34.9	33.6	32.8	33.2	32.1	184/137	70	- 6	Hypertension. Enlarged heart Rheumatic heart disease. Mitral stenosis and insufficiency
L.H. 351566 F. 44	2/ 1/44	64	37.25	33.87	35.3	34.5	34.4	34.4	34.8	33.8	35.2	32.2	32.8	32.3	34.3	166/111	74	+ 2	Hypertension. Enlarged heart
E.C. 380212 F. 46	3/24/44	118	37.34	34.17	34.6	35.5	34.4	34.8	34.2	33.7	34.9	33.7	33.2	32.8	34.4	182/116	72	+ 12	Essential hypertension. Enlarged heart

TABLE I--CONT'D

CASE HISTORY NO., SEX, AGE (YR.)	DATE	PERIPHERAL (C.C./ M. ² / MIN.)	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHTED SKIN TEMPERATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1	2	3	4	5	6	7	8	9	10	11				
Data Relating to Twenty-Five Male Subjects—Cont'd																			
W. C. 375325 M. 48	1/ 5/44 1/ 7/44	62 70	37.27 37.10	34.30 33.97	35.3 35.0	35.1 34.8	34.5 34.3	34.7 34.3	34.4 33.4	34.2 34.2	35.0 34.8	33.7 32.9	33.5 33.2	33.2 33.9	34.4 34.5	198/113 193/112	66 66	- 1 - 2	Hypertension. Slightly enlarged heart
R. L. 376206 M. 19	2/10/44	81	36.81	33.97	34.7	34.4	34.6	33.9	33.6	35.1	33.9	33.3	32.5	33.4	212/136	82	- 5	Hypertension. Chronic glomerulonephritis. Enlarged heart	
S. McD. 95209 M. 48	12/ 3/43	25	37.11	33.52	34.9	33.5	33.7	33.5	33.9	34.2	33.1	32.2	33.0	32.5	177/113	68	-11	Hypertension. Enlarged heart	
V. K. 308001 M. 51	4/ 5/44	25	36.94	32.25	34.4	34.3	32.8	32.2	33.4	32.3	32.7	32.0	30.1	30.2	31.5	243/121	91	+33	Hypertension. Enlarged heart. Arteriosclerotic heart disease. Hypothyroidism
G. L. 351331 M. 31	3/16/43 3/22/43	136 108	37.36 37.11	34.89 34.51	35.6 35.4	35.3 35.0	35.1 35.0	34.9 34.5	34.8 34.4	35.3 35.1	34.6 34.0	34.7 34.4	33.7 33.2	34.4 34.4	156/108 163/113	68 67	+ 6 + 3	Essential hypertension	
Average—men Average age = 36 yr. Standard deviations about the means		61 54	37.27 0.24	33.74 0.60	34.8 0.7	34.7 0.6	34.3 0.8	34.4 0.8	34.1 0.7	33.8 0.8	34.5 1.0	33.4 0.9	32.8 1.1	32.5 1.0	32.1 1.7	184/122 28/15	76 11	+ 4	
Data Relating to Thirty-One Female Subjects																			
E. E. 375575 F. 56	2/10/44	69	37.16	33.66	34.2	34.1	34.3	33.7	34.3	33.2	34.0	32.9	33.2	33.2	33.3	193/124	82	- 2	Hypertension. Enlarged heart Cerebral hemorrhage
R. S. 381016 F. 50	4/ 4/44	16	37.23	33.17	34.7	34.1	32.9	32.8	32.9	33.0	34.6	32.0	32.8	32.8	33.5	182/118	71	- 4	Essential hypertension

M. I. 309586 F. 26	1/19/44 2/ 7/44	15 25	37.10 37.08	32.24 33.11	34.2 34.2	32.7 33.2	32.2 33.0	32.2 33.2	33.1 33.6	32.8 33.0	34.6 34.9	30.5 31.1	30.2 31.8	34.5 32.7	33.3 34.7	159/124 168/108	84 64	+ 6 - 8	Cushing's syndrome. Hypertensive cardiovascular disease. Generalized arteriosclerosis. Arteriosclerotic heart disease. Myocardial infarct. Enlarged heart. Aortic insufficiency. Fibrosis of lungs
A. B. 373431 F. 43	12/14/43	94	37.72	34.19	33.6	35.0	34.3	34.7	34.4	33.5	34.8	33.5	33.4	33.7	35.2	232/187	82	+28	Hypertension. Enlarged heart. Chronic glomerulonephritis
M. K. 373552 F. 39	12/ 8/43	36	37.99	33.14	34.9	34.5	34.3	33.6	33.6	32.8	34.5	32.1	31.6	31.4	32.1	186/129	98	+13	Hypertension. Enlarged heart
S. S. 373586 F. 47	12/10/43 12/15/43	10 9	37.98 38.29	32.90 33.00	34.7 34.9	34.3 34.4	33.9 33.9	33.3 33.5	33.5 34.0	32.3 33.3	33.9 34.2	33.2 32.4	32.1 32.2	31.5 31.4	28.9 29.4	180/114 174/111	72 68	+ 9 + 5	Hypertension. Enlarged heart
J. M. 373987 F. 66	11/11/42	89	37.31	32.98	34.2	33.4	33.8	33.7	32.8	32.6	34.0	31.5	32.2	32.1	32.7	154/85	72	+ 6	Arteriosclerotic heart disease. Hypertension. Enlarged heart
L. M. 312091 F. 37	11/19/42	68	37.54	33.78	34.5	34.4	34.6	34.3	34.1	34.0	34.2	33.5	32.1	32.9	33.4	172/109	66	- 4	Hypertension
N. L. 340799 F. 25	10/22/42	55	37.42	33.24	34.3	33.9	34.8	34.2	32.7	32.7	32.8	33.0	31.6	32.5	32.0	164/111	72	+ 1	Chronic glomerulonephritis. Hypertension
M. T. 229483 F. 49	3/ 8/44 3/ 9/44	27 54	37.02 36.96	33.12 33.25	34.6 34.7	34.4 34.8	34.3 33.9	34.5 34.5	33.6 34.1	33.1 32.8	34.2 34.1	32.7 32.7	32.6 32.8	31.5 32.0	28.1 28.6	133/84 132/84	76 75	+ 4 + 4	Essential hypertension
Average—women Average age = 39 yr. Standard deviations about the means		52 43	37.27 0.38	33.46 0.68	34.5 0.6	34.3 0.7	34.3 0.9	34.0 0.9	33.6 0.7	33.1 0.6	34.2 0.7	32.6 1.0	32.3 0.9	32.4 0.9	32.2 2.2	182/120 30/19	75 8	+ 2	
Average—men and women Age = 38 yr. Standard deviations about the means		57 43	37.27 0.33	33.59 0.63	34.7 0.6	34.5 0.7	34.3 0.8	34.2 0.9	33.8 0.8	33.4 0.8	34.3 1.6	33.0 1.0	32.5 1.0	32.4 0.9	32.1 1.9	183/121 32/16	76 9	+ 3	
Average—normal men Standard deviations about the means		73 30	36.79 0.16	33.74 0.33	34.4 0.3	34.2 0.4	34.1 0.5	34.2 0.5	33.8 0.5	33.7 0.5	34.4 0.5	33.2 0.7	33.2 0.7	33.2 0.5	32.7 1.9	105/71 5/5	61 7	- 5 10	

TABLE I—CONT'D

CASE, HISTORY NO., SEX, AGE (YR.)	DATE	PERIPHERAL (C.C./ MIN.)	BLOOD FLOW	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHED SKIN TEMPERATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS	
						1	2	3	4	5	6	7	8	9	10	11					
<i>Data Relating to Thirty-One Female Subjects—Cont'd</i>																					
E. L. 233250 F. 43	4/27/39 5/6/39			37.24 37.12	32.70 32.61	33.8 33.4	34.0 34.2	33.5 33.8	33.3 33.3	32.0 32.5	32.7 32.8	33.4 33.2	32.0 31.0	31.4 30.9	31.3 31.4	32.4 32.4	220/130 214/112	-27 +5	Essential hypertension. cardiac enlargement	Slight	
M. N. 231336 F. 33	4/28/39			37.39	32.53	34.3	34.4	34.4	34.5	33.7	33.8	34.2	33.5	32.7	31.2	32.5	230/130	+16	Hypertension.	Enlarged heart	
T. W. 213332 F. 39	2/29/40			37.64	35.34	35.6	36.3	36.5	36.5	35.8	35.1	35.6	35.5	33.7	34.0	33.5	227/129	71	+22	Hypertension.	Enlarged heart
M. H. 250110 F. 33	11/10/39			37.08	33.73	34.8	34.5	35.2	35.2	33.6	33.4	33.5	33.4	31.6	31.4	27.6	219/129	96	+8	Hypertension. largement	Slight cardiac en
A. P. 385261 F. 23	6/15/44			36.83	33.67	34.9	35.2	34.2	33.8	33.9	33.1	34.3	32.8	31.9	33.2	33.1	171/115	71	+7	Hypertension	
C. F. 256800 F. 33	6/12/44			36.88	33.02	34.1	33.8	34.0	32.9	33.3	32.8	34.6	31.7	32.3	32.4	31.9	131/96	74	-10	Hypertension	
D. B. 304744 F. 30	9/13/41			37.16	33.05	34.2	34.7	35.6	34.5	32.7	32.2	31.9	33.7	32.1	31.8	27.0	146/120	76	-9	Essential hypertension	
R. M. 382365 F. 52	3/31/44			36.73	33.43	34.4	34.3	34.3	33.1	33.5	33.1	34.3	32.7	32.1	32.8	33.5	208/125	67	+7	Hypertension.	Enlarged heart
R. McK. 376816 F. 46	2/17/44 2/18/44	29 44		37.01 36.92	33.43 32.98	34.9 34.9	34.1 33.4	33.9 33.4	33.4 33.4	33.3 32.7	33.1 32.5	34.6 34.3	32.4 30.9	32.7 31.0	32.5 32.2	33.5 32.8	170/108 155/106	76 72	-13 -18	Essential hypertension. heart. Encephalopathy	Enlarge

hypertensive subjects than in the normal subjects (Table I, Fig. 1). Although these differences are not significant statistically, it appears more than chance that in both men and in women with hypertension the upper part of the body is warmer and the lower part is cooler. It would not be expected that the means should take such a precise arrangement if it were the result of chance. The reduction in temperature of the lower part of the body is greater than the elevation of temperature of the upper part of the body, so that the average of the weighted skin temperature is, on the whole, less in the hypertensive patients.

Blood Pressure.—The average of the blood pressures for this hypertensive group was 183/121 (Table I).

Pulse Rate.—The average of the pulse rates of this hypertensive group was 76 per minute (Table I).

Basal Metabolic Rate.—The average of the basal metabolic rates of the group with hypertension was +3 per cent, while that of the normal subjects was -5 per cent¹⁸ (Table I, Fig. 2).

PRE-OPERATIVE HYPERTENSIVES BASAL METABOLIC RATE

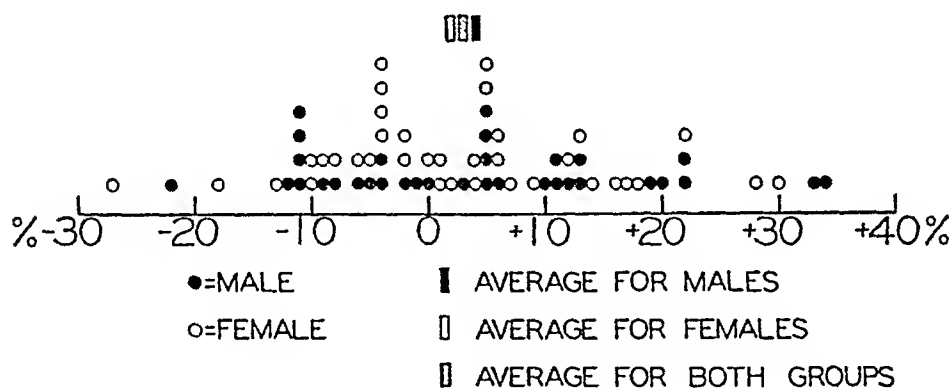


Fig. 2.—In this figure is shown the scatter of the basal metabolic rates of the patients whose data are shown in Fig. 1.

DISCUSSION

These observations show certain differences in the peripheral blood flow and rectal and skin temperatures of hypertensive subjects as compared with those of young normal subjects. We did not have a comparable mixed group of normal young men and women for comparison but have used the young male group on which observations have already been reported. On comparison of the male component of this group of hypertensives with the group of normal men, it was found that these show the same trends as in the average of the male and female hypertensive groups, but the differences were slightly less marked. The trend is for a lower peripheral blood flow in the hypertensive group than in normal subjects, that the hand (Area 7), abdomen (Area 4), and arm so. The room temperature of 27° C. was chosen in order to have vasodilatation present in each series. The rectal temperature was higher in the hypertensives

with the group of normal young adults, or in the peripheral blood flow of the men of the hypertensive group as compared with the women with hypertension.

Average Rectal Temperature.—The average rectal temperature for the hypertensive patients was 37.27°C ., with a range of 36.68°C . to 38.29°C ., while the average rectal temperature of normal young subjects was 36.79°C ., with a range of 36.32°C . to 37.24°C . Although on statistical analysis the difference is not significant, the rectal temperature of hypertensive patients was higher than that of normal persons (Table I, Fig. 1); most of the hypertensive patients have rectal temperatures above 37° , while most of the normal persons have rectal temperatures below 37° .

Average Weighted Skin Temperature.—The average weighted skin temperature of the whole body of the hypertensive patients was 33.59°C ., with a range of 32.01°C . to 35.34°C ., while the average for the normal young subjects was 33.74°C ., with a range of 32.65°C . to 34.36°C .¹⁸ (Table I, Fig. 1.) In short the mean of the average weighted skin temperature of the hypertensive patients was cooler than that of normal young subjects, but the difference is not statistically significant.

Temperature of Hands.—The average of the temperatures of the hands in hypertensive patients was 34.3°C ., with a range of 31.2°C . to 35.4°C ., while the average temperature for the normal young subjects was 34.4°C ., with a range of 32.8°C . to 35.5°C .¹⁸ (Table I, Fig. 1). That is to say the hand temperatures in the group with hypertension were essentially the same as those of the normal subjects, but the fluctuations were greater.

Temperature of the Feet.—The average of the temperatures of the feet in hypertensive patients was 32.1°C ., with a range of 27.0°C . to 35.2°C ., as compared with an average temperature of 32.7°C ., with a range of 26.0°C . to 34.3°C ., in normal subjects¹⁸ (Table I, Fig. 1). In short, the foot temperature of hypertensive patients was slightly colder, but because of the wide fluctuations of the foot temperature in individuals (emotional effects, etc.) the difference is not statistically significant.

Temperature of Forehead.—The temperature of the forehead in hypertensive patients averaged 34.7°C ., with a range of 32.2°C . to 35.7°C ., as compared with an average of 34.4°C ., with a range of 33.8°C . to 34.9°C ., for the normal group¹⁸ (Table I, Fig. 1). In short, the forehead was slightly warmer in hypertensive patients than in normal young subjects, but the difference is not statistically significant.

Temperatures of Areas of the Body Considered as Regions.—When the temperature of the individual areas of the body are considered in relation to each other, it is seen that the temperature of the upper part of the body, including the forehead (Area 1), upper chest (Area 2), and lower chest (Area 3), is warmer in hypertensive than in normal subjects.¹⁸ The temperature of the abdomen (Area 4), arm (Area 5), and hand (Area 7) is essentially the same in those with hypertension as in normal subjects. The temperature of the lower part of the body, including the forearm (Area 6), upper thigh (Area 8), lower thigh (Area 9), leg (Area 10), and foot (Area 11), however, are colder in the

eral blood flow and rectal temperature in these subjects, nor between systolic or diastolic levels of blood pressure and peripheral blood flow.

The average of the basal metabolic rates for the whole series of hypertensive patients was +3 per cent, compared with an average of -5 per cent in normal men. The range in both from minus to plus basal metabolic rates was slightly greater in the hypertensive series, but the basal rate in hypertension does not appear to be appreciably greater than in normal subjects¹⁸ or in other patients with heart disease before the onset of failure.²⁰ These observations are in agreement with those of Shapiro²¹ who found that the basal metabolic rate in hypertension falls within accepted normal limits.

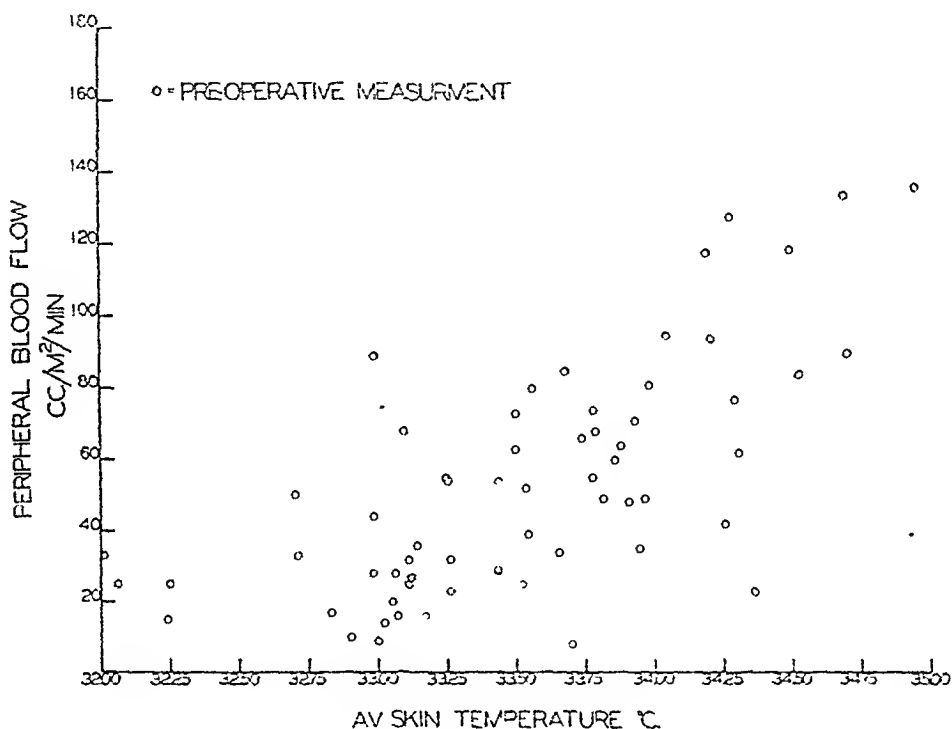


Fig. 3.—In this figure the peripheral blood flows of all patients (Table I) are plotted against the corresponding average skin temperatures. A linear correlation is demonstrated, which, however, is not as close as the correlation after operation.⁵

It is of interest to compare the data relating to the male subjects in this younger group of hypertensive patients with the hypertensive male patients in the later decades.²² The peripheral blood flow in the younger subjects was *lower* than in the older ones but not significantly so statistically. The rectal and average weighted skin temperatures were *higher* in younger hypertensive patients, but again the difference was not great enough to be significant. With a few exceptions the temperatures for all the areas of the body were greater in the younger group of hypertensive patients. The exceptions were the temperatures of the hand (Area 7), which were decreased, and of the lower thigh (Area 9) and leg (Area 10), which were the same. The differences, however, were not significant. Although on statistical analysis the differences are not significant, there is the pattern in which there appears to be a trend toward lower peripheral blood flow and greater rectal and skin temperatures in young hypertensive patients than in those with hypertension who reach the later decades. In short,

than in normal subjects, but the average weighted skin temperature was less. The hands were of the same temperature in the hypertensive patients as in the normal persons, but the feet were colder. The foreheads of the hypertensive patients were slightly warmer than normal, but the difference was not sufficient to explain the flush which hypertensive patients exhibit clinically.

It is seen that the upper part of the body is warmer in hypertensive than in normal subjects, that the hand (Area 7), abdomen (Area 4), and arm (Area 5), have the same temperature in hypertensive and normal individuals; and that the lower part of the body, including the forearm (Area 6), upper thigh (Area 8), lower thigh (Area 9), leg (Area 10), and foot (Area 11), is colder than normal. The reduction in temperature in the lower part of the body is greater than the elevation of temperature in the upper part. As a consequence, the average weighted skin temperature is colder in hypertensive patients than in normal subjects when the whole group is considered; for the male group alone, however, the average skin temperature was the same as in the normal group. The warmer upper part indicates increased peripheral blood flow to this part, the normal temperature of the middle part of the body indicates an essentially normal amount of blood flow in this area, and the cold lower part of the body indicates a decreased amount of blood allotted to the peripheral circulation in this part. Reduction in temperature of the colder part is so much more marked than the rise in temperature of the warmer part, taking into consideration weighting of different parts of the body, that the total amount of blood allotted to the whole periphery of the body is decreased as compared with a normal subject. There appears then to be vasodilatation in the upper part of the body and vasoconstriction in the lower part. As a consequence, the skin cannot dissipate efficiently the increased amount of heat produced, and increased heat storage and rise in rectal temperature result.

Abramson and Fierst¹⁰ found the resting blood flow to the forearm and leg of hypertensive patients by the venous occlusion method was greater while that in the hand was less than in a normal group they observed. This method measures the total amount of blood going to that part in cubic centimeters per minute per 100 c.c. of limb volume. On the other hand, the method we have used measures the average amount of blood allotted to the periphery of the whole body in cubic centimeters per square meter of body surface per minute, for a depth of about 1 cm. below the skin surface. Steele and Kirk¹⁹ in a study of nine hypertensive patients did not find any difference from normal in the skin temperature in the areas from which they recorded the temperature. Differences in the general plan and technique of the two sets of experiments may account for these differences: our patients were nude and remained basal throughout the morning the observations were made; moreover the larger number of patients in our series may give a wider spread of variations.

In these patients with hypertension there is a linear correlation between peripheral blood flow and the average weighted skin temperature (Fig. 3) since the higher average skin temperatures were associated with higher values for the peripheral blood flow. There was no demonstrable correlation between periph-

tension of pheochromocytoma²⁷ in which there is reason to believe that there is vasoconstriction due to the discharge of epinephrine into the blood stream, the effects would be expected to be generalized. In accord with this theory, we found²⁷ that the skin in most parts of the body was colder than normal, with a low average weighted skin temperature and very cold forehead, hands, legs, and feet.

SUMMARY

The peripheral blood flow and average skin and rectal temperatures have been measured under basal conditions in 56 patients suffering from arterial hypertension. A modification of the method of Hardy and Soderstrom was used. Observations were made at an environmental temperature of 27° C. and 50 per cent humidity.

1. The average peripheral blood flow for the group is slightly decreased as compared with normal subjects, but the difference does not appear to be statistically significant; the range is essentially the same as in normal subjects.

2. The rectal temperature is higher than in normal subjects, the temperature being over 37° C. in most hypertensive subjects and under 37° C. in the normal control group.

3. The average weighted skin temperature is lower than that in normal subjects, but the difference is not significant statistically.

4. In hypertensive patients the temperature is higher than normal in the upper part of the body, is near the normal level in the middle part of the body, and is cooler than normal in the lower part, especially in the feet.

5. There were no significant differences between the peripheral blood flow or rectal or skin temperatures of the men and those of the women with hypertension.

6. The level of the peripheral blood flow is unrelated to the level of the systolic or diastolic blood pressure in individual patients, and a linear correlation between peripheral blood flow and blood pressure level was not apparent.

7. In these patients with hypertension there was a linear correlation between the level of peripheral blood flow and the average weighted skin temperature, in that the higher the skin temperature the higher the peripheral blood flow.

8. The basal metabolic rate in hypertensive patients is within the normal range.

9. The hypertension of patients observed in this study exhibits different characteristics from those prevailing in coarctation of the aorta and in pheochromocytoma, in which the local skin temperatures are, respectively, warmer and cooler than normal.

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the deviation from the normal is not as great in older individuals with hypertension as in the younger hypertensive patients.

It is of interest to compare the measurements in patients suffering from essential hypertension with those made in patients in whom hypertension was a consequence of coarctation of the aorta.²³ The data in the two sets of observations are not strictly comparable, because in the latter group observations were made at 25° C., while in the observations now being reported the room temperature was 27° C. In the patients with coarctation of the aorta the average weighted skin and rectal temperatures were higher than those in normal subjects at the same room temperature, and, moreover, the temperatures of the skin of all the eleven areas of the body which were measured were *higher* than those in normal subjects. The hypertension of coarctation of the aorta is associated with warm feet and that of essential hypertension is associated with cool feet. The cardiac output in coarctation of the aorta is increased²⁴ so that there is available an increased amount of blood for allotment to the periphery of the body.

Starr and his associates²⁵ and Stewart²⁶ have shown that in certain patients with hypertension without heart failure the cardiac output is within the normal range, while in others the cardiac output is decreased. Starr found that those patients with the smaller cardiac output had smaller hearts than those with large outputs. In some, the cardiac output was smaller than that in subjects with normal hearts. This reduced cardiac output achieves the maintenance of hypertension without increase in the heart's basal work. Since measurements of cardiac output were not available in the group of patients we are now reporting, correlation with the trend toward decrease in peripheral blood flow could not be made.

The manifestations of the high blood pressure of essential hypertension are also different from those in the hypertension of pheochromocytoma. In a patient suffering from such a tumor, observations²⁷ pointed to marked generalized peripheral vasoconstriction. The peripheral blood flow was decreased even though the basal metabolic rate was +48 per cent which would be expected to increase the peripheral blood flow (Stewart and Evans²⁸). The average weighted skin temperature was decreased (32.45° C.), and the temperature of the hands and feet was very cold (31.10° C. and 26.80° C., respectively). Because the body could not dissipate the increased amount of heat produced, there was heat storage and a high rectal temperature resulted.

These observations indicate that the elevation of arterial pressure in hypertensive individuals does not depend on constriction of the arterioles of the skin, subcutaneous tissue, and muscle to the depth of 1 cm. below the surface. Steele and Kirk¹⁹ arrived at a similar conclusion. While on the average the peripheral blood flow may be decreased in hypertension, there is no correlation between the peripheral blood flow and the level of blood pressure. Moreover, if the rise in blood pressure were dependent on such vasoconstriction, which would presumably be generalized, it would be difficult to explain the tendency to increase in warmth of the upper part of the body and decrease in temperature of the lower part in hypertensive individuals. On the other hand, in the hyper-

AN EVALUATION OF THE USE OF MULTIPLE VERSUS SINGLE PRECORDIAL LEADS, IN CONJUNCTION WITH THE THREE LIMB LEADS, FOR PRACTICAL CLINICAL ELECTROCARDIOGRAPHY

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THE value of precordial leads in clinical electrocardiography has been clearly established through numerous studies and extensive practical experience since the independent observations of Wolferth and Wood¹ and Wilson and his co-workers² were first reported in 1932. Differences of opinion and uncertainty still exist, however, concerning the most reliable and practicable method of utilizing precordial leads for clinical purposes, particularly with regard to the number of precordial positions that need to be explored and the proper location for the remote electrode. On the other hand, it is quite generally accepted at the present time that the traditional three limb leads³ should be retained as the basic leads for clinical use, and that in conjunction with these one or more precordial leads should be employed. Although investigations dealing with "unipolar"⁴ and "augmented unipolar"⁵ limb leads, as well as with esophageal leads,⁶ have aroused considerable interest during recent years, additional studies are needed to demonstrate how practical these special leads are for ordinary clinical use.

In 1938, the Committee of the American Heart Association for the Standardization of Precordial Leads^{7, 8} described in detail the techniques for recording and agreed upon the terminology for identifying single and multiple precordial leads of various accepted types; but the Committee was unwilling at that time to decide on any standard procedure for the use of precordial leads in clinical practice. More recently this Committee⁹ has expressed the opinion that a single precordial lead from the region of the cardiac apex, or from any other part of the precordium, is inadequate and has stated that three is the least number of precordial leads that can be regarded as satisfactory for general purposes. However, notwithstanding this and other recent developments¹⁰⁻¹³ with regard to the superiority of multiple over single precordial leads, electrocardiograms which combine the three limb leads with only a single precordial lead are still used extensively. Probably by virtue of its originally demonstrated utility,^{14, 15} the single precordial lead most commonly employed is an apical lead taken with the precordial electrode located at the outer border of the cardiac apex and with the remote electrode located on the left

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tion of the relative merits of these two combinations of leads for use in practical clinical electrocardiography.

MATERIAL AND METHODS

Clinical and electrocardiographic examinations were made on each of 224 adult persons. These included an adequate number of normal controls and different examples of the commonly encountered forms of cardiac abnormality. No case was included on the basis of the comparative electrocardiographic findings per se.

Each of the 224 test subjects was thoroughly studied clinically to determine the presence or absence of cardiac abnormality and the etiological basis for heart disease, when present. The classification of the individuals studied, as determined by the clinical examination, is shown in Table I. Sixty-eight test subjects had no clinical evidence of heart disease and were utilized as normal controls, whereas 156 test subjects had definite clinical evidence of cardiac abnormality. In the latter group, 53 had hypertensive heart disease, 36 had experienced a recent myocardial infarction, 43 had coronary arteriosclerosis without indications of remote or recent myocardial infarction, 12 had chronic valvular heart disease of rheumatic or syphilitic origin, 5 had congenital cardiac lesions of a sort compatible with adult life, 4 had pulmonary disease with evidences of acute or chronic cor pulmonale, 2 had thyrotoxic cardiac disease, and 1 had a beri-beri heart.

TABLE I. CLINICAL CLASSIFICATIONS OF 224 INDIVIDUALS STUDIED

<i>Total with no clinical evidences of heart disease (normal controls)</i>	68
Hypertensive heart disease	53
Recent myocardial infarction	36
Arteriosclerotic heart disease	43
Valvular heart disease of rheumatic or syphilitic origin	12
Congenital cardiac lesions (adult type)	5
Pulmonary disease with acute or chronic cor pulmonale	4
Thyrotoxic heart disease	2
Beriberi heart disease	1
<i>Total with definite clinical evidences of cardiac abnormality</i>	156
Total individuals studied	224

One or more electrocardiograms were taken on each of the 224 persons studied. All tracings were made with the subjects in the reclining position. In every case Leads I, II, III, and IVF, and CR leads from the six recognized precordial positions⁸ were recorded.

In analyzing the individual electrocardiograms, the three limb leads were interpreted as showing abnormality when significant cardiac arrhythmias were noted; when the P-R intervals or the QRS complexes were of greater duration than 0.20 and 0.10 second, respectively; when the QRS complexes showed low voltage in all three limb leads; when Q waves greater than 25 per cent of the amplitude of the R waves were present in Leads I or II; when broad S waves were noted in Leads I and II; when the S-T segments were displaced more than 1 mm. from the isoelectric line in either direction in any limb lead; when

leg. The combination of Leads I, II, III, and IVF has been so widely used in clinical practice over the past decade that many physicians still erroneously believe that this particular series of leads constitutes the modern standard electrocardiogram, that the use of multiple precordial leads is a supplementary procedure for the more scientific study of selected cases, and that the need for multiple precordial leads can be anticipated in particular situations. In the light of recent experience and current informed opinion, these assumptions are not justified. One is forced to conclude, therefore, that the advantages of multiple rather than single chest leads and the necessity for their use in clinical practice have not been sufficiently emphasized.

Despite the reluctance of many cardiologists to adopt multiple precordial leads in ordinary clinical practice, among those who have studied precordial leads most fully,⁹ there are no important disagreements regarding the superiority of multiple over single precordial leads for general purposes. On the other hand, the problem of the proper location for the remote electrode has become involved in the current discussion^{16, 17} over the validity of the Einthoven equilateral triangle hypothesis^{18, 19} that the human body acts, with respect to the three limb leads, essentially as a homogeneous volume conductor. Accordingly, there are differences of opinion on the best location for the remote electrode. The problem of the best location for the remote electrode needs further study and must be resolved before any single standard procedure for the routine use of precordial leads in clinical electrocardiography can be agreed upon. However, we have long felt²⁰ that the advantages of multiple over single precordial leads remain essentially valid, in most circumstances at least, for any of the currently recognized locations of the remote electrode. We feel very strongly, therefore, that it is the intrinsic superiority of multiple over single precordial leads that should be given special emphasis and wider attention, entirely apart from the uncertainties of the proper location for the remote electrode.

The study herein presented was planned to provide additional data regarding the practical advantages of employing multiple rather than single precordial leads, in conjunction with the three limb leads, in routine electrocardiographic diagnosis. For the purposes of this study, the IVF type of single precordial lead was employed because of its widespread popularity. The CR type of multiple precordial lead was used for comparison. A critical comparison of the CR, CL, CF, and V types of multiple precordial leads was not attempted and is not herein implied, since our particular interest was to provide a practical evaluation of multiple versus single precordial leads.

The present report deals, therefore, with the study of a large number of test subjects, some with and some without heart disease. On each subject, in correlation with the clinical findings, the electrocardiographic information furnished by Leads I, II, III, and IVF was compared with the information supplied by the three limb leads in conjunction with CR leads from the six recognized precordial positions.⁸ From summaries and further analyses of these data, an effort was made to derive a statistical and inferential evalua-

these 156 cardiac patients who showed abnormalities of one sort or another, when a particular lead or combination of leads was included for the analysis, is given in Table II. Fourteen (9 per cent) of these 156 patients showed electrocardiographic findings which were of entirely normal character for all leads of the ten-lead record. One hundred forty-two (91 per cent) of these cardiac patients were found to show definite abnormalities in one or more leads of this ten-lead record. In seven (4.5 per cent) of the 156 patients, the only electrocardiographic abnormality in any of the ten leads was an inversion of the T waves in Lead IVF. Analysis of the nine-lead record consisting of Leads I, II, III, and CR₁ to CR₆, inclusive, and of the six-lead record consisting of precordial leads CR₁ to CR₆, inclusive, revealed that both of these combinations showed electrocardiographic abnormalities in 135 (86.5 per cent) of the 156 cases. Likewise, the combination of Leads I, II, III, CR₁, CR₃, and CR₅, inclusive, showed abnormality in one or more leads for 135 (86.5 per cent) of these cardiac patients. The three limb leads were found to be abnormal for 119 (76.3 per cent) of the 156 patients with heart disease, whereas the four-lead record consisting of Leads I, II, III, and IVF showed abnormalities for 126 (80.7 per cent) of these cases. This last figure includes the seven cases in which inverted T waves in Lead IVF were the only abnormality observed in the ten-lead record. The numbers and percentages of these cardiac patients showing electrocardiographic abnormalities in leads from the individual precordial positions varied widely. Lead IVF was found to be abnormal for 91 (58.3 per cent) of the 156 cases, including the seven patients whose records showed T-wave negativity in Lead IVF as the only abnormality; whereas Lead CR₅ showed abnormality for 117 (75 per cent) and Lead CR₆ showed abnormality for 112 (71.8 per cent) of the cardiac patients. For each of the other CR leads, the number of patients showing electrocardiographic abnormality varied between 38 cases (24.3 per cent) for CR₁, to 66 cases (42.3 per cent) for CR₄ (Table II).

TABLE II. SUMMARY OF THE NUMBERS AND PERCENTAGES OF THE 156 PATIENTS WITH CLINICAL EVIDENCES OF HEART DISEASE WHO SHOWED ELECTROCARDIOGRAPHIC ABNORMALITIES WHEN PARTICULAR LEADS OR COMBINATIONS OF LEADS WERE UTILIZED FOR ANALYSIS

COMBINATION OF LEADS OR INDIVIDUAL LEADS ANALYZED	NUMBER OF PATIENTS SHOWING ABNORMALITY IN ONE OR MORE OF SUCH LEADS	PERCENTAGE OF TOTAL 156 PATIENTS
Leads I, II, III, IVF, CR ₁ to CR ₆	142	91.0
Leads I, II, III, CR ₁ to CR ₆	135	86.5
Leads CR ₁ to CR ₆	135	86.5
Leads I, II, III, CR ₁ , CR ₃ , CR ₅	135	86.5
Leads I, II, III	119	76.2
Leads I, II, III, IVF	126	80.7
Lead CR ₁	38	24.3
Lead CR ₂	48	30.8
Lead CR ₃	53	35.2
Lead CR ₄	56	42.3
Lead IVF	91	58.3
Lead CR ₅	117	75.0
Lead CR ₆	112	71.8

T waves were diphasic, isoelectric, or inverted in Lead I or II; or when any combination of these findings was observed. Deviations of similar character in Lead III were regarded as abnormal only when significant associated changes could be detected in Lead I or II. The three limb leads were not regarded as abnormal when a benign arrhythmia (such as an occasional ectopic complex), or slight slurring of the QRS complexes, or slight to moderate axis deviation was the only feature observed.²² Lead IVF and the six CR leads were interpreted as showing abnormality when significant arrhythmias were noted, or when the contours of the QRS complexes, the S-T segments, or the T waves in any one of these precordial leads, or the sequences of such contours in Leads CR₁ to CR₆, inclusive, deviated significantly from the normal forms as reported by Deeds and Barnes.²³ In judging whether definitive diagnostic patterns were shown by, or superior information could be derived from, different combinations of the precordial and limb leads, criteria for interpretation as set forth by Wilson et al.,^{12, 17} Wood and Selzer,¹⁰ Ashman and Hull,²⁴ Pardee,²⁵ and Katz²⁶ were used.

In the group of 68 test subjects with no clinical evidences of heart disease and the group of 156 test subjects with definite clinical evidences of cardiac abnormality, the number and percentages who showed electrocardiographic normality or abnormality in particular leads or combinations of leads were computed. In each case the record combining Leads I, II, III, and IVF was compared with the record which included the three limb leads and precordial leads CR₁ to CR₆, inclusive, in order to see which of these two combinations of leads revealed more definitive diagnostic patterns or supplied superior electrocardiographic information. Statistical summaries of these data were then attempted and were made when the comparisons appeared valid.

RESULTS

For the 68 subjects who were used as normal controls, the electrocardiographic findings in all leads of the ten-lead record were used in every case for this study. No comparative statistical summary concerning the demonstration of definitive diagnostic patterns by different combinations of the available leads could be derived from the records on these 68 control subjects, since in each case any combination of leads produced the definitive pattern of normality, in accordance with the criteria which we applied. However, the findings of normal contours and sequences of contours in the CR leads from the six precordial positions yielded a more complete definitive pattern of normal precordial potentials for each case than did the contours in the single Lead IVF. Consequently, for these 68 control subjects, the individual records consisting of the three limb leads in conjunction with the six CR leads did provide, inferentially at least, information on which to base the interpretation of electrocardiographic normality, which was superior to that given by the individual records which combined Leads I, II, III, and IVF.

For the 156 patients with definite clinical evidence of cardiac disease, the electrocardiographic findings yielded significant data when the ten-lead record of each case was analyzed. A summary of the numbers and percentages of

useful for revealing abnormalities affecting preponderantly the right auricle or right ventricle, that the CR₅ and the CR₆ leads were particularly useful for revealing abnormalities affecting preponderantly the anterolateral aspects of the left ventricle, and that the CR₃ and the CR₄ leads were necessary to complete the definition of the precordial electrical field. More specifically, in one instance of syphilitic heart disease, Leads CR₁ and CR₂ were of value in detecting a cardiac arrhythmia of auricular origin (two-to-one auriculoventricular block), where, because of the blending of P and T waves, the presence of such an arrhythmia was not shown by the three limb leads, by Lead IVF, or by the other CR leads. In two patients with clinical evidences of long-standing mitral stenosis, in one instance of chronic cor pulmonale due to extensive pulmonary fibrosis, and in one case of interauricular septal defect, the CR₁ and CR₂ leads yielded evidence indicating right ventricular hypertrophy, and in two patients with coronary arteriosclerosis the presence of right bundle branch block was detected, when in each of these cases the findings noted in Leads I, II, III, and IVF were not regarded as definitely abnormal. Leads CR₃ and CR₄ in one instance revealed the presence of an acute antero-septal myocardial infarction, the electrocardiographic diagnosis of which would have been missed had the tracing included only Leads I, II, III, and IVF, or, for that matter, the other CR leads. In eight additional cases, with hypertensive or arteriosclerotic heart disease, Leads CR₅ and CR₆ revealed electrocardiographic evidences of left ventricular hypertrophy, or of nonspecific myocardial abnormality (inverted T waves), which were not detected by Leads I, II, III, and IVF. Thus, for 16 (10 per cent) of the 156 patients with heart disease, the combination of Leads I, II, III, and IVF had to be interpreted in each as being within normal limits, whereas, from one or another of the multiple CR leads, the electrocardiographic findings permitted either a nonspecific or a definitive diagnosis of abnormality. Moreover, in four subjects with hypertensive heart disease, in 12 with acute myocardial infarction, in nine with arteriosclerotic heart disease, and in one case of patent ductus arteriosus, the electrocardiographic findings in Leads I, II, III, and IVF were abnormal but could not be considered clear-cut or specific; evidence of right or left ventricular hypertrophy, right or left bundle branch block, or the presence and extent of an acute anterior, anterolateral, or posterolateral myocardial infarction, were revealed only by the six CR leads. Thus, for an additional 26 (17 per cent) of the 156 patients with heart disease, compared to the findings shown by the three limb leads or by Lead IVF, the multiple CR leads gave superior information which permitted a more definitive electrocardiographic diagnosis to be made. It should be added that even for the 93 (60 per cent) of the 156 cases with heart disease wherein the three limb leads were regarded by us as being adequate to yield all the truly essential interpretative information that could be derived even from the ten-lead record, the six CR leads were in most instances definitely useful for corroborating and clarifying the character and extent of the electrocardiographic abnormality.

Our effort to determine, from the individual electrocardiograms on the 156 cardiac patients, the number of cases showing definitive diagnostic patterns by the different combinations of leads failed to yield a summary which we were willing to accept as valid in its implications. This failure resulted because in some of the cases difficulties were encountered in deciding or agreeing on whether the particular patterns shown by different combinations of the available leads could be considered definitive. For this same reason, there was disagreement about the number of cases in which the diagnosis indicated by a particular combination of leads could be made no more specific than "abnormal form of ventricular complex indicating myocardial damage." In this attempted analysis, however, it became impressively evident that the three limb leads constituted for practical purposes the indispensable basis for electrocardiographic diagnosis, and that the six CR leads, as well as the single Lead IVF, served largely to correct, modify, or enhance the diagnostic impressions derived from the three limb leads alone. The three limb leads were found to be definitely superior to the CR or IVF leads for indicating specifically the presence of a posterior or basal myocardial infarction.

When the individual electrocardiograms on the 156 cardiac patients were analyzed to determine the relative superiority of different combinations of the available leads for supplying practical electrocardiographic information, an apparently valid summary was derived by employing the three limb leads as the basic electrocardiogram and by determining the number of cases wherein added useful information was afforded by Lead IVF on the one hand, or by the six CR leads on the other. Of the 37 cases in which Leads I, II, and III were normal, in 14 cases Lead IVF and the six CR leads were likewise normal; in 7 additional cases Lead IVF showed inverted T waves as the only abnormality in the ten-lead records; whereas the six CR leads showed the only abnormalities and definitive diagnostic information in 16 cases. Of the 119 cases in which Leads I, II, and III were abnormal, in 93 cases the three limb leads yielded all the truly essential information that could be derived from the ten-lead record on each case; for none did Lead IVF yield any useful added information, whereas for 26 cases the six CR leads gave additional information. Therefore, of the total of 156 cases with clinical evidences of cardiac abnormality, all leads of the available ten-lead records were found to be normal in 14 cases (9 per cent), despite the definite evidences of cardiac abnormality indicated by the clinical examinations; in 93 cases (59.6 per cent) the three limb leads proved adequate to supply all the truly essential interpretative information that could be derived from the ten-lead records; in seven cases (4.5 per cent) Lead IVF alone of the available leads gave information indicating electrocardiographic abnormality; and in 42 cases (26.9 per cent) the six CR leads gave information regarding abnormalities and definitive diagnosis over and beyond that supplied by Leads I, II, III, and IVF.

With regard to the type of electrocardiographic information furnished by the different CR leads in the individual cases with clinical evidences of heart disease, we found in general that the CR₁ and CR₂ leads were particularly

It might be inferred as well, though with some reservation, that in the cases without clinical evidence of cardiac abnormality the three limb leads were adequate to indicate electrocardiographic normality. These results, therefore, tend to explain the great reluctance of many cardiologists to add any material number of additional leads to the traditional limb leads record and strongly support the view that the three limb leads must remain the basic and indispensable leads for practical clinical electrocardiography at the present time. On the other hand, in this study the six precordial leads added appreciable electrocardiographic information. In 27 per cent of the patients with clinical evidences of heart disease, the six CR leads gave additional information of value regarding abnormalities, and/or definitive diagnosis over and beyond that supplied by Leads I, II, III, and IVF. In the individuals without clinical evidences of cardiac abnormality, moreover, the multiple CR leads lent added assurance to the diagnosis of electrocardiographic normality, and it was felt in the majority of these cases that the relative size and position of the heart in the chest could be more accurately inferred from the six CR leads.

In our material, however, it was observed that the single precordial Lead IVF, despite its current widespread popularity, added relatively little information to that indicated or suggested by the three limb leads alone. Although in seven of the 156 patients with heart disease T-wave negativity in Lead IVF was the only observed abnormality in the ten-lead record, this abnormality obviously resulted from a difference in the character of the electrical potentials occurring at the left leg and at the right arm, since all the CR leads were normal in these seven cases. Therefore, the exact significance of this finding, in terms of its detecting intrinsic cardiac abnormality rather than the effects of cardiac position,²⁷ or of its indicating the superiority of CF- over the CR-type of precordial leads, is uncertain and remains for other studies to determine. Additional objections to Lead IVF as the only precordial lead were also noted in this study. One of the most potent is the difficulty of placing the precordial electrode just beyond the region of the true cardiac apex in certain patients, especially those with enlarged left ventricles. Improper placing of this electrode may actually vitiate whatever value a single precordial lead has for electrocardiographic diagnosis. Moreover, our observations in this study suggest that, particularly where left ventricular hypertrophy is present, the field of electrical potential preponderantly reflecting left ventricular activity may in some instances be located farther to the left than the anatomic apical area.

In this study the electrocardiographic record combining the three limb leads with precordial leads CR₁, CR₃, and CR₅ revealed abnormalities in the same number of patients with heart disease as did the record combining the three limb leads with precordial leads CR₁ to CR₆, inclusive. The former combination did not reveal with the same certainty the character of the precordial electrical field, and in a fair number of instances would have resulted in an incorrect or less definitive interpretation than the latter. Objective evidence to support this view was not derived because we were unwilling to

In the 156 cases with cardiac disease, 98 of the individual patients showed clinical evidences of rather severe congestive heart failure, and moderate or marked enlargement of the left ventricle was shown by the physical examination or by x-ray films or fluoroscopy. In more than one-third of these 98 cases, the electrocardiographic contours noted in Lead IVF suggested that this lead was not, in fact, directly reflecting the field of electrical activity resulting from the left ventricle. This seemed evident in some of these latter cases even though Lead IVF had been taken with the exploring electrode carefully located at the precordial point immediately lateral to the region of the cardiac apex. In all such instances, Leads CR₅ or CR₆, taken with reference to fixed anatomic locations on the chest, were found definitely superior to Lead IVF, because, by more clearly reflecting the field of electrical activity resulting from the enlarged left ventricle, they made possible a more accurate orientation and interpretation. Indeed, in this study the relatively poor showing obtained with Lead IVF seemed to result largely from the inherent difficulty of applying the precordial electrode at the true cardiac apex; even in instances where the three limb leads indicated quite clearly the presence of left ventricular hypertrophy, the contours noted for Lead IVF were often not abnormal. On the other hand Lead IVF did often show evidences of myocardial abnormality, or definitive diagnostic patterns of abnormality. However, the results obtained with Lead IVF in this study were relatively poor statistically because this lead often did not reveal evidences of abnormality affecting the right or left ventricle when either the three limb leads or the multiple CR leads, or both, showed such abnormality quite clearly.

In comparing the findings noted for the combination of Leads CR₁, CR₃, and CR₅ with the information furnished by the combination of Leads CR₁ to CR₆, inclusive, we found that each of these combinations showed electrocardiographic abnormalities in the same number of patients with heart disease (see Table II). On the other hand, for the entire group of cases with heart disease, it was not possible to select any combination of three CR leads which would permit as reliable and definitive an evaluation of the precordial potential variations as was derived from the use of all six CR leads. This is readily understandable when one considers the variability of the size and position of the heart in the chest, as well as the variability in the type of electrocardiographic contours noted from the different precordial positions.

DISCUSSION

The results of this study are in keeping with the previously reported findings of others¹⁰⁻¹² and lend support to the indications for the use of precordial leads. In addition, they provide, at least in part, a statistical comparison of the information derived from the three limb leads alone, and from the three limb leads in conjunction with single or multiple precordial leads. It should be emphasized that for 60 per cent of the cases with cardiac disease the three limb leads proved adequate to supply all the truly essential interpretative information that could be derived from the ten-lead records herein employed.

5. For the 156 cases with clinical evidences of cardiac abnormality, the six CR leads in conjunction with the three limb leads were found definitely superior to Leads I, II, III, and IVF for providing information both as to abnormality and type of abnormality present. Statistical data to support this view are given.

6. It is concluded that precordial leads should be employed in combination with the three limb leads for practical clinical purposes, and that the most reliable and complete electrocardiographic information is afforded when leads from the six precordial positions are routinely used for this purpose.

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compare statistically merely suggestive with more clear-cut electrocardiographic findings. On the other hand, the combination of precordial leads CR₁ to CR₆, inclusive (without limb leads), also revealed abnormalities in the same number of cases with heart disease as were revealed by the combination of the three limb leads with the six CR leads; but, in the entire group of cases with heart disease, the former combination certainly did not yield the same amount of definitive diagnostic information as did the latter. Because of the variability of the findings indicated by the individual CR leads for the entire group of cases, we believe that it is impossible to employ with any reasonable success less than the six recognized precordial leads since that would require an anticipatory knowledge of the probable location and type of the abnormality to be found. Moreover, in this study we observed that any attempt to reduce the number of precordial leads, even to as few as three, often resulted in loss of the fundamental advantage in the use of precordial leads which is derived from the exploration of the entire precordium.

The objection has been raised that, in comparison with the additional information derived, the use of six rather than a single precordial lead in conjunction with the three limb leads, entails for practical clinical purposes too much additional effort in recording and interpreting the resulting electrocardiogram. From our results in the present study, we are not in sympathy with such objections. Rather, we believe that precordial leads have definite practical value for clinical use, that a single precordial lead is woefully inadequate for proper orientation and interpretation of precordial electrical potentials, and that whenever complete electrocardiographic information is desired, one cannot in the present state of knowledge afford to do less than combine the three limb leads with a record which explores the entire precordium, using leads from the six recognized precordial positions.

SUMMARY AND CONCLUSION

1. Clinical and electrocardiographic examinations were made on 224 individuals. Judged by the clinical findings, sixty-eight were found to be free of heart disease and 156 had definite evidences of cardiac abnormality.

2. On each test subject, electrocardiograms were utilized which included Leads I, II, III, and IVF and CR leads from the six recognized precordial positions and which were analyzed statistically and inferentially to determine the comparative value of multiple versus single precordial leads for use in conjunction with the three limb leads for practical clinical electrocardiography.

3. For the entire 224 cases, the three limb leads were found essential as the basic leads for the electrocardiographic study, and were found to be of fundamental value in the electrocardiographic interpretations.

4. For the 68 subjects with normal hearts, the individual records consisting of the three limb leads in conjunction with the six CR leads provided information on which to base the interpretation of electrocardiographic normality which was superior to that provided by the individual records which combined Leads I, II, III, and IVF.

Clinical Reports

ABNORMAL ELECTROCARDIOGRAM FOLLOWING RECOVERY FROM PAROXYSMAL TACHYCARDIA

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THE case described below presents an interesting and rather unusual electrocardiogram following recovery from paroxysms of tachycardia. This consists of the spreading out of the T waves to produce a prolonged Q-T interval, associated with inversion of the T waves and depression of the corresponding S-T segments. Similar cases have been described in the literature, but they seem to be quite rare.

Graybiel and White¹ reported a case of ventricular tachycardia in 1934 in which the electrocardiogram taken after recovery showed inversion of the T wave in Leads II and III. There was a gradual return to normal within a few months. They found no similar electrocardiogram in their records. This patient had no apparent organic heart disease. While the Q-T interval was not mentioned specifically, the tracings show it to be about 0.46 second. Six weeks later the interval had been reduced to 0.40 second. (This figure is not entirely accurate since the 0.04 second marker line does not appear on the record.)

Schulten² reported one case in which the electrocardiogram after recovery from ventricular tachycardia showed a prolonged Q-T interval, with inversion of the T waves in all leads. During the following four weeks, first Lead I, then, successively, Leads II and III of the electrocardiogram gradually returned to normal.

Cossio and his co-workers³ reported four cases. Three of these cases showed depressed S-T segments and negative T waves in Leads II and III; the other showed negative T waves in Leads I and II. At autopsy one case showed cardiac dilatation, but there was no involvement of the coronary vascular system and no focal necrobiosis. The changes were believed to be due to enlargement of the heart or right ventricular strain and not to the presence of a real coronary insufficiency. Campbell⁴ agrees that such electrocardiographic changes do not indicate organic disease but are a completely reversible process indicating some degree of exhaustion or strain of the heart muscle.

Geiger⁵ recently reported a case in which this type of electrocardiogram was encountered after recovery from supraventricular tachycardia. The patient had had two attacks ten years apart. No clinical evidence of heart disease

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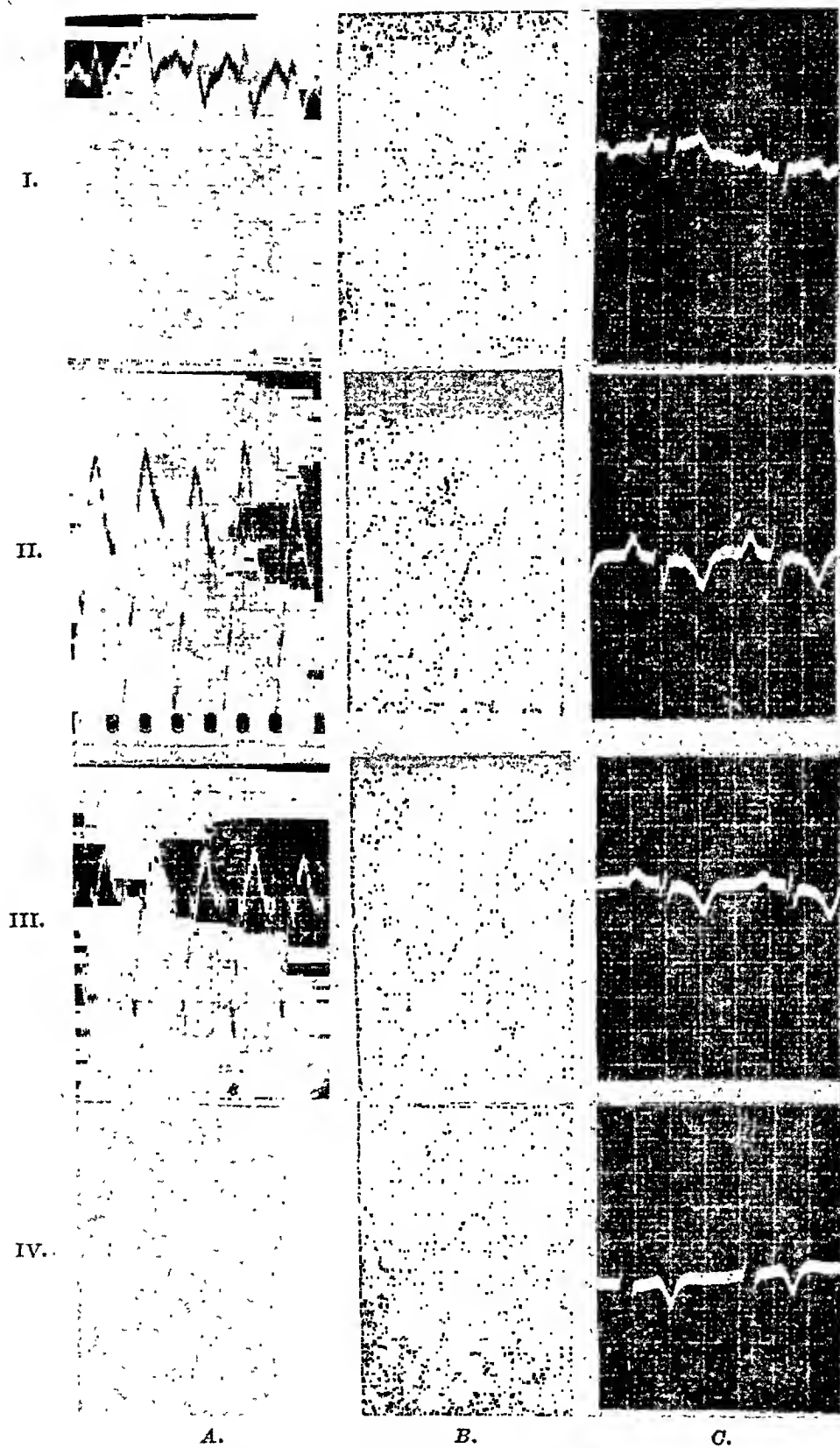


Fig. 1.—A, Tracing taken on first admission, July 3, 1942, shows paroxysmal tachycardia. The chest lead is missing. B, Tracing taken after restoration of sinus rhythm, July 4, 1942, showing peculiar T waves and prolonged Q-T interval. C, Tracing taken July 8, 1942, showing normal Q-T interval; T waves are still inverted.

could be demonstrated after recovery, and the author warns of the danger of interpreting the changes in the electrocardiogram seen after recovery as being due to coronary thrombosis.

CASE REPORT

First Admission.—A 19-year-old white youth was admitted to the hospital on July 3, 1942, because of palpitation of the heart. The attack had started suddenly, without apparent cause.

He gave a history of similar attacks in the past, the first having occurred at the age of 12 years. This attack subsided spontaneously after a few hours. Two years later, during a basketball game, he had another attack. During the next five years he had frequent attacks, usually following exertion, but sometimes occurring without apparent cause. There was no history of previous illness nor of any rheumatic manifestations. Except for these attacks, he had been in good health and was a normal vigorous boy. He smoked about three packages of cigarettes daily.

On examination the patient did not seem acutely ill. The respirations were 28 per minute but not labored. There was no cyanosis. The arteries of the neck were seen to be pulsating rapidly, and the veins appeared slightly full. The apical impulse of the heart was visible in the sixth intercostal space, 1 cm. outside the midclavicular line. There was no palpable thrill, nor was there an audible murmur. The heart sounds were very rapid and had a "tie-tac" quality. The heart rate was about 200 per minute. The lungs were entirely clear. The liver extended 2 fingerbreadths below the right costal margin and was not tender. There was no edema. The temperature was normal. Urinalysis showed 1 plus albumin.

An electrocardiogram taken on admission showed paroxysmal tachycardia,* with a ventricular rate of 210 per minute (Fig. 1, A). One hour after the administration of 6 grains of quinidine sulfate by mouth, the heart rate had decreased to 120. Due to an error, 30 additional grains of quinidine sulfate were given in the next six hours. An electrocardiogram taken at this time (Fig. 1, B) showed regular sinus rhythm with very peculiar T waves. Besides being inverted in Leads II and III, they were spread out so that the Q-T interval was 0.48 second, as compared with the commonly accepted normal maximum of 0.39 second. There was also slight depression of the S-T segments in these leads, and the P waves were very prominent.

Examination of the heart after sinus rhythm had been restored showed the apex beat outside the mid-clavicular line. A harsh systolic murmur, loudest in the fourth intercostal space to the left of the sternum, was heard over the entire precordium.

Because he felt well, the patient insisted on leaving the hospital. Four days later he returned for another electrocardiogram (Fig. 1, C). There was still inversion of the T waves and depression of the S-T segments in Leads II and III, but the Q-T interval had decreased to 0.36 second, which is well within normal limits. In the chest lead the T wave had become inverted and the inversion of the P wave had disappeared. In Leads II and III the P wave was still prominent.

Second Admission.—Before a fourth electrocardiogram could be taken, the patient developed another paroxysm of tachycardia. This attack had started during a wrestling bout. The physical findings were the same as on his original admission. The blood pressure was 90/70, and the pulse rate was about 200 per minute. The electrocardiogram taken on re-admission (Fig. 2, A) again showed paroxysmal tachycardia. The urinalysis and blood count were normal. The mouth temperature was 99.6° F. Six grains of quinidine sulfate were given. Two hours later the patient began to sweat, and he vomited several times. His blood pressure was 80/60. Four hours after the medication the cardiac rhythm became normal and he was placed on a maintenance dose of 3 grains of quinidine sulfate three times a

*Although the tachycardia appears to be ventricular in origin, this cannot be positively established. Since the type of tachycardia has no bearing on the findings that are being emphasized, no further attempt will be made to identify the origin of the tachycardia.

DISCUSSION

The two interesting changes in the electrocardiogram after recovery from tachycardia are a prolonged Q-T interval and an inversion of the T waves. In some reported cases the T waves in all the limb leads were inverted; in others only the T waves of Leads I and II or II and III were inverted. The present case falls into the latter category.

White and Mudd⁶ established a normal range for electrical systole as determined by the Q-T interval. They found that this interval depends on the heart rate and is more prolonged at lower rates. For instance, at a heart rate of 160, the Q-T interval varied between 0.21 and 0.24 second; while at a heart rate of 60, the variation was from 0.26 to 0.44 second. These are extreme ranges and most of the cases fell near the mid-point, averaging about 0.34 second with slow rates. They also found prolongation of the Q-T interval in association with such electrocardiographic abnormalities as bundle branch block, paroxysmal tachycardia of both the auricular and the ventricular type, and ventricular premature contractions. Among the extracardiac factors which may lengthen electrical systole are hypocalcemia^{6, 7} and hypopotassemia.⁸

Inverted T waves are seen in many conditions; no attempt will be made to enumerate them all. A common condition associated with T-wave inversion is myocardial infarction, and this may confuse the physician when confronted by a patient who develops a sudden ectopic rhythm, usually associated with precordial distress and dyspnea. I believe that the electrocardiogram of recovery from tachycardia is not typical of the electrocardiogram of myocardial infarction, and if the characteristics are kept in mind, confusion will be avoided. It is unfortunate that more prolonged follow-up in this case was not possible. It would have been interesting to see whether or not the T-wave inversions reverted to normal as they have done in other reported cases. It must be remembered, however, that in many of these cases the patients had normal hearts, while the patient here reported probably had a congenital patent interventricular septum, and it is possible that Leads II and III of his normal electrocardiogram would show inverted T waves indicative of right ventricular enlargement, even though there was no right axis deviation.

SUMMARY

A case showing an abnormal electrocardiogram following recovery from paroxysmal tachycardia is reported. The abnormalities consist of a prolongation of the Q-T interval and inversion of some or all of the T waves, with depression of the associated S-T segments. It should be recognized that such changes can be the result of paroxysmal tachycardia and are not necessarily an indication of the presence of serious organic disease. A brief review of the relevant literature is included.

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day. A tracing made the following day (Fig. 2, B) was similar to the one taken after cessation of tachycardia on his first admission. (A technical error produced an inverted Lead IVF.) The Q-T interval was again 0.48 second, as it was in Fig. 1, B. A teleroentgenogram showed moderate enlargement of the heart, especially pronounced in the apical region.

Again the patient insisted on leaving the hospital. He was advised to remain under medical supervision.

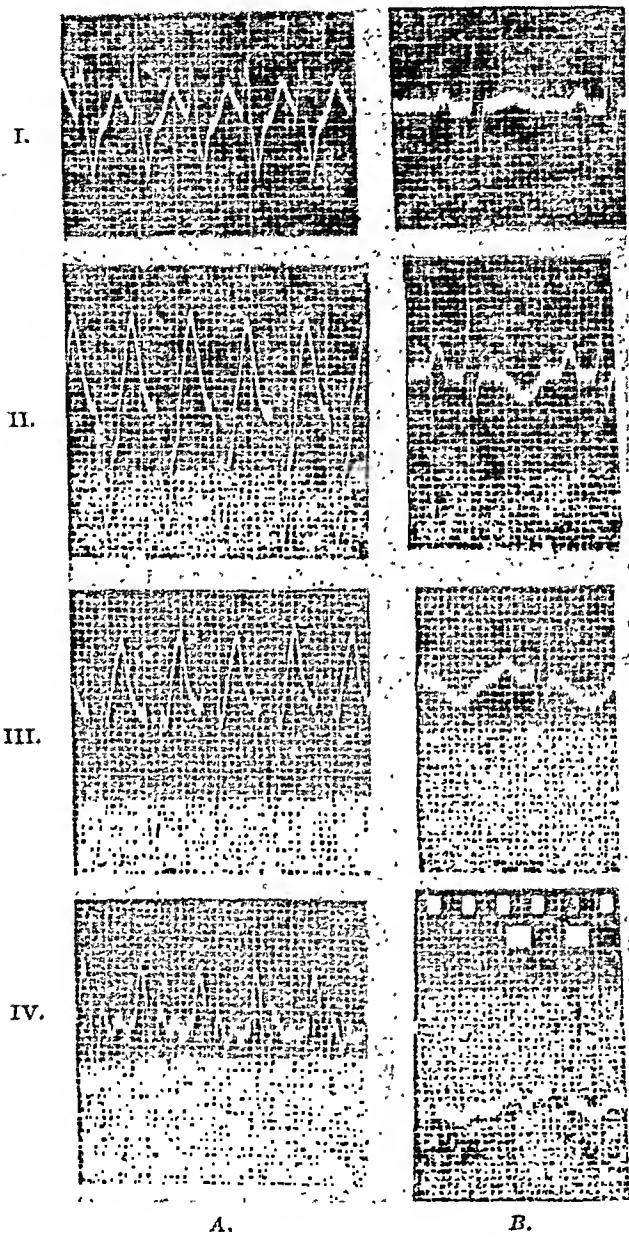


FIG. 2.—A, Tracing taken on second admission, July 12, 1942, identical with Fig. 1, A. B, Tracing taken July 13, 1942, after restoration of sinus rhythm, identical with tracing 1, B.

Third Admission.—He was readmitted on Aug. 3, 1942, with another paroxysm of tachycardia which had begun while he was at rest. Eighteen grains of quinidine sulfate administered within a period of eight hours restored the cardiac rhythm to normal. He had not been under a doctor's care nor had he taken any medicine since his last dismissal. He insisted on leaving the hospital before any observations could be made, and shortly thereafter he left the city.

SUBACUTE BACTERIAL ENDOCARDITIS SUCCESSFULLY TREATED WITH PENICILLIN

REPORT OF A CASE

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LEWISBURG, PA.

F. H. J., a 31-year-old white man, was incarcerated in the United States Northeastern Penitentiary, Lewisburg, Pa., on Oct. 4, 1944. He was assigned to the work of handling steel on the night shift of prison industries. He worked steadily at this job for slightly more than three months. On the evening of Jan. 13, 1945, he reported to the prison hospital, complaining of shortness of breath and palpitation of three days' duration. He stated that he had "low blood pressure" and that six months previously an Army induction board had classified him 4F because of this condition. Further questioning revealed that he had had acute rheumatic fever at the age of 11 and again at the age of 16 years. At the age of 27 years a fainting spell led to several weeks' hospitalization. He was told by his attending physician at that time that he had suffered a heart attack.

The patient was therefore admitted to the prison hospital for study. Upon admission he appeared well developed and well nourished and was in no acute distress. His weight was 182 pounds. He was ambulatory and well oriented. The temperature was 98° F., the pulse was 100, and the respirations were 20 per minute. The blood pressure was 134/50. The skin was sallow. There was no lymphadenopathy. The eyes showed an old chorioiditis. There was extensive gingivitis and dental caries. Examination of the heart revealed a forceful apex thrust in the fifth intercostal space 12 cm. to the left of the midline; there were no palpable thrills; the rate was 100, with a regular rhythm. The apical first sound was accentuated and roughened, followed immediately by a short high-pitched systolic murmur. The aortic second sound was muffled and partially obscured by a to-and-fro systolic and diastolic murmur which was transmitted into the neck vessels. There was no ankle edema, no hepatic engorgement, no distention of the jugular veins, and no râles in the lung bases. Duroziez's sign was equivocal. An electrocardiogram showed widening of the QRS in all leads, inverted P, deep Q, inverted T, and T, elevated RS-T, depressed RS-T, and left axis deviation. A teleroentgenogram of the chest showed the heart to be at the upper limit of normal size, with slight prominence of the left ventricle.

The patient was observed for two weeks. During this time he was ambulatory, slept without difficulty on one pillow, remained entirely afebrile, and had no complaints. On Jan. 31, 1945, when arrangements with the prison administration for sedentary occupation had been completed, he was discharged. The diagnosis on discharge was inactive rheumatic heart disease with aortic stenosis and insufficiency and possible early mitral insufficiency.

Nine days later, the patient again reported to the hospital complaining of a cold and sore throat which had been present for the previous forty-eight hours. Fever and pains in the hips, knees, ankles, and wrists had existed for twenty-four hours. Examination revealed: temperature, 100; pulse rate, 100; respiration, 24; blood pressure, 134/50. The skin was warm and flushed, but there were no petechiae. The cervical lymph nodes were shotty and tender. The pharyngeal mucous membranes were injected. The left ankle and right hip were tender to touch but were not warm, reddened, or swollen. The cardiac findings were the same as had been noted previously. The blood count showed: red blood cells, 5,390,000; hemoglobin, 12.6 Gm.; white blood cells, 8,250; polys, 64 per cent, lymph-

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siderably during and after treatment. It seems most likely that this represented a true Flint's murmur, particularly since a very recent teleroentgenogram of the heart showed no change in size or shape of the left auricle as compared with the previous picture that would indicate the development of mitral stenosis. The patient's weight, which had fallen from 182 pounds on admission to 157 pounds, was 190 pounds at last report. During therapy the only change in the blood picture was a transient eosinophilia of 5 to 9 per cent. There was never any profound anemia or leucocytosis. The urine showed no abnormalities at any time. The sedimentation rate remained between 31 and 38 mm. per hour during treatment but had fallen to 9 mm. per hour seven weeks later.

Although at least six months must elapse before it can be stated with finality that this patient has been clinically and bacteriologically cured of his disease, his blood has been sterile for ten weeks; no treatment has been given for seven weeks. While the prognosis must still be guarded, the outlook for complete bacteriologic cure in this case is good. Despite our enthusiasm over a new and apparently efficacious drug for a hitherto fatal disease, we must remember that this patient has recovered with further damage to an already deformed heart. This will not only limit his physical activity but also increase the likelihood of reinfection.

ADDENDUM

At the time of his discharge from prison, in March, 1946, the patient was still bacteriologically negative.

ocytes, 21 per cent; monocytes, 13 per cent; eosinophiles, 2 per cent. The sedimentation rate (Wintrobe) was 31 mm. per hour. The urinalysis was negative. The patient was admitted to the hospital with a tentative diagnosis of an acute exacerbation of rheumatic fever. He was put to bed and given full doses of sodium salicylate, which relieved the joint symptoms. After ten days of symptomatic therapy, however, the fever still persisted, averaging 100.4° F. The pulse consistently remained over 100. A blood culture taken on the thirteenth hospital day, showed on the eighteenth day a pure culture of *streptococcus viridans* with eight colonies per cubic centimeter. A second culture, taken on the twentieth day, was again positive for *streptococcus viridans*. Three additional cultures taken prior to the administration of penicillin were also positive.

On the twenty-fifth hospital day, cardiac changes were first evident; a diastolic thrill and a low-pitched rumbling diastolic murmur were detected at the apex; the apical systolic murmur had become longer; the blood pressure was 134/10.

On the thirty-second hospital day the patient developed in his left conjunctiva his first and only petechia. The following day he suddenly developed severe precordial pain radiating to the left axilla; his left arm suddenly became numb and partially paralyzed. Use of the arm returned slowly over a ten-day period.

Penicillin therapy was started on the thirty-sixth day. In vitro sensitivity tests were made at the beginning of penicillin therapy in the following manner:

A loopful of a forty-eight-hour broth culture of the patient's blood was inoculated into each of several flasks of brain-heart infusion broth containing penicillin in concentrations ranging from 0.0005 unit per cubic centimeter to 0.5 Oxford unit per cubic centimeter. After a seventy-two-hour incubation period it was found that there was complete inhibition of growth of the organisms in those flasks whose penicillin concentration was 0.05 unit per cubic centimeter or greater, while growth was noted in all flasks whose penicillin concentration was lower than 0.05 unit per cubic centimeter.

During the first ninety-six hours, 770,000 units of penicillin were given by continuous intravenous drip. Each 100,000 units were dissolved in 1 L. of 5 per cent dextrose in distilled water. Because of the severe local reaction, however, the penicillin was administered intramuscularly, 30,000 units being given every three hours for three days. The dosage was then lowered to 15,000 units every three hours and was maintained at this rate for three days but, because of a slight afternoon temperature rise with the smaller dose, was then raised to 20,000 units every three hours. This dosage was continued for eight days and then increased to 30,000 units every three hours for five and one-half days. Although 3,440,000 units were given intramuscularly, the patient tolerated the injections extremely well. A concentration of 10,000 units per cubic centimeter was employed. When treatment was terminated, on the fifty-eighth day, a total of 4,210,000 units had been given continuously over a twenty-three and one-half day period.

After six days of treatment the teeth were x-rayed. An abscess was found at the root of the lower right first bicuspid. The tooth was extracted, but unfortunately no culture was taken from the abscess.

Blood cultures which, before treatment, had been persistently positive for *Streptococcus viridans*, became sterile twenty-four hours after the initiation of treatment. Cultures taken every seventy-two hours during the administration of penicillin and at weekly intervals since, have been sterile to date. Seven weeks have elapsed since treatment was discontinued.

The temperature, which had averaged 100.4° F. prior to the initiation of penicillin therapy, fell rapidly to normal and remained normal except for afternoon rises of less than 1° F. After nine days of therapy the patient became completely afebrile and has remained so. The pulse likewise slowed from between 100 and 110 to between 80 and 90, and remained at this rate even when the patient became ambulatory. The diastolic blood pressure, which had fallen from its original level of 50 mm. to 10 mm., rose gradually and at the termination of therapy stood again at 50 millimeters. Likewise, the diastolic apical bruit which developed during the first part of hospitalization diminished in intensity con-

This treatment was discovered by chance when a patient who had Buerger's disease was bitten and attended the local Institute daily for vaccine therapy. After several injections he noted that he no longer had to ride but could easily walk to the Institute, a distance of 1 km., without pain. Repetition of the treatment in additional cases has given good results. The favorable effect of the antirabies toxin is considered comparable with that of cobra toxin.

LAPLACE.

Blair, H. A., and Wedd, A. M.: The Action of Cardiac Ejection on Venous Return. *Am. J. Physiol.* 145: 528 (Feb.) 1946.

The authors discuss their views regarding the mechanical relationships between cardiac ejection, lung air pressure, chest wall movements, and venous return. Observations on which their conclusions are based included synchronous recording of the electrocardiogram and volume curves of the neck, chest, and upper abdomen. It is stated that the excess of arterial outflow over venous inflow to the chest during systole tends to create a partial vacuum of about 15 mm. Hg in the lungs, but collapse of the chest wall permits only about 0.5 mm. Hg of this pressure to be realized. This partial vacuum is not nearly so important in assisting venous return as the negative intrapleural pressure. Cardiac failure may be expected to increase the promotion of venous return by causing the accumulation of blood in the lungs, which decreases lung volume and diminishes lung movement. In mitral stenosis, even in the absence of failure, the venous return to the chest frequently appears to exceed the arterial outflow during systole. This is indicated by the finding that in these cases the chest may expand during systole rather than collapse.

LAPLACE.

Nahum, L. H., and Hoff, H. E.: The Configuration of Epicardial and Endocardial Extrasystoles in the Chest Leads. *Am. J. Physiol.* 145: 615 (Feb.), 1946.

Extrasystoles were recorded from the epicardial and endocardial surfaces of the right and left ventricles of dogs. Four leads were recorded: transthoracic, IVF, IVR, and the central terminal lead of Wilson. It was found that when the stimulating electrodes were aligned with the transthoracic leads or were immediately subjacent to the exploring electrode in the chest leads, there was no difference between epicardial and endocardial extrasystoles, the initial deflections of both showing a simple QS complex. When the stimulating electrodes were placed otherwise, the extrasystoles were of differing patterns according to their source.

It is inferred that the electrocardiogram as recorded by limb and chest leads does not reveal the existence of currents associated with the conduction of excitation from the endocardium and epicardium.

LAPLACE.

Evans, W. F., and Graybiel, A.: Electrographic Evidence of Cardiac Complications in Infectious Mononucleosis. *Am. J. M. Sc.* 211: 220, 1946.

The authors studied 100 patients with infectious mononucleosis and concluded that four of the 100 patients had some type of cardiac complication associated with the disease. This opinion was based chiefly on the presence of electrocardiographic changes. The principal changes were progressive lowering of the height of the QRS complexes and the T waves. In two of the four patients the T waves became actually inverted. These changes gradually disappeared and the tracings ultimately became normal. In addition to the electrocardiographic evidence of cardiac involvement, there were some confirmatory clinical evidences in three patients, although the clinical signs were not striking. The heart rate was slow in proportion to the temperature in all three patients. In one patient a pericardial friction rub was present and in another there was some cardiac enlargement. None of the patients had cardiac failure. The presence of a friction rub in one case, as well as the type and course of the electrocardiographic changes led the authors to suspect that the pericardium rather than the myocardium was the chief site of involvement. A fifth patient, who had massive pericardial effusion for which no etiology other than infectious mononucleosis could be found, lent some support to this view.

Abstracts and Reviews

Selected Abstracts

Warren, J. V., Stead, E. A., Jr., and Brannon, E. S.: The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization, *Am. J. Physiol.* 145: 458 (Feb.) 1946.

This paper is an appraisal of certain features of the catheter technique of cardiac output determination as based on the authors' experience with the method in over 500 subjects. Variation between the oxygen content of paired consecutive samples of arterial blood did not exceed 0.4 volume per cent and in 77 per cent of the determinations was 0.2 volume per cent or less. In 111 instances in which comparative determinations were made of blood from the right atrium, 78 per cent varied no more than 0.4 volume per cent, but the remainder varied as much as 2.3 volumes per cent. In 25 instances of similar determinations on ventricular blood, 80 per cent varied no more than 0.4 volume per cent, and the remainder varied as much as 1.8 volumes per cent. Comparison of the oxygen content of atrial and ventricular blood samples in 19 patients showed variation of 0.4 volume per cent or less in 11 patients, 1 volume per cent or less in 11 patients and 1.2 volumes per cent in two patients. Check of 42 duplicate samples of expired air was within 10 per cent in 31 instances and as much as 20 per cent in the remaining 11 instances. It appears possible that some of the variation between consecutive samples of ventricular blood are due to changes in cardiac output rather than technical errors. The errors in the values for oxygen consumption seem partly technical and partly real. It is concluded that the catheter method is more accurate in situations in which the arteriovenous oxygen difference is great. The errors involved seem to be random rather than systematic. Results obtained with this method are more valid when groups rather than individuals are studied, as the inaccuracies in individual values for cardiac output are occasionally large. LAPLACE.

Elbel, E. R., and Green, E. L.: Pulse Reaction to Performing Step-Up Exercise on Benches of Different Heights. *Am. J. Physiol.* 145: 521 (Feb.) 1946.

The present study was conducted to determine whether variation in the height of the bench or stool significantly affects the pulse reaction of normal subjects to the step-up exercise. The subjects were seventy-two healthy aviation students. Each subject was tested ten times, twice on each of five benches which were 12, 14, 16, 18, and 20 inches in height. Two periods of exercise were used for each bench, one for thirty seconds and one for sixty seconds. The exercise was performed at a rate of 24 steps per minute.

The pulse rates for the thirty seconds immediately after exercise depended upon the height of the bench and the duration of the exercise. After the thirty-second exercise, the average increment was 3.7 beats per minute greater for each additional 2-inch increase in height of the bench; after the sixty-second exercise, the average increment was 5.6 beats per minute. The pulse rates taken one minute after exercise were practically the same for the various heights of the benches and durations of exercise. LAPLACE.

Nini, Mehreh, and Saadeh: Buerger's Disease. *Rev. méd. franç. du Moyen-Orient* 3: 391 (May) 1945.

Four cases of Buerger's disease are presented, together with a discussion of the symptomatology, diagnosis, and treatment. Therapy of one of the reported cases, which appeared responsible for conspicuous clinical improvement, was the use of antirabies vaccine.

reported, in which a definite history of a virus infection in the mothers during pregnancy has been obtained. In all but two of these cases, the offending virus disease was rubella. In all but five cases, the rubella occurred before the third month of pregnancy.

Of the 136 patients, 80 per cent had unilateral or bilateral cataracts; 62 per cent were mentally deficient; 57 per cent had heart disease, and 54 per cent had a combination of cataracts and heart disease. It is difficult to evaluate the significance of these reported cases because it is not known how often malformations occur without being the result of virus infection.

One hundred and twenty cases of congenital anomalies studied by the authors revealed five cases with a history of rubella occurring during pregnancy. This incidence of 4.2 per cent is ten times higher than that occurring in the population at large. The evidence suggests that a relationship exists between the maternal rubella and the development of congenital anomalies.

Also presented are three instances in which virus infection occurred in the ninth month of pregnancy and the children were normal. It is suggested that the virus infection must occur during early pregnancy in order to produce a congenital anomaly. The authors quote Goodpasture, who suggested that young, relatively undifferentiated cells are more easily affected by the virus than mature cells.

BELLET.

Ash, R.: Precordial Leads in Childhood; Comment on the Presence of Double Upward Deflections in Leads From the Sternal Region of Normal Children. *Am. J. Dis. Child.* 70: 277 (Nov.-Dec.), 1945.

This study analyzes single tracings obtained from 150 children whose electrocardiographic examination included precordial leads (CF_2 and CF_4). The children ranged in age from 9 days to 15 years, the average being 7.6 years and the age of greatest frequency being 8 years. The most striking variation from the electrocardiogram of an adult was in the T waves, which were usually inverted in leads near the sternum, but were also not infrequently inverted in leads in the region of the apex. The frequency of inversion diminished with the increased age of the child, depending on the age of the child and the position of the electrode on the chest wall. Negative, diphasic, or positive T waves may therefore be normal in childhood.

A P wave of amplitude greater than 2 mm. in Lead CF_2 or 1 mm. in CF_4 , whether upright, diphasic, or inverted, or a duration greater than 0.08 second was considered abnormal.

The presence of a Q wave in CF_2 was considered abnormal. In CF_4 the presence of the Q wave less than 25 per cent of the amplitude of the R wave probably has no significance. An absent R wave or one smaller than 1 mm. in either lead was considered abnormal.

Triphasic complexes (double upward deflection) and M-shaped QRS complexes have been described as always abnormal in Leads CF_2 and CF_4 . Ash observed that in normal children, triphasic complexes may be observed in the region to the left of the sternum. Such complexes were considered abnormal in only six children in whom the transient nature of the distortion seemed proved by the presence of diphasic complexes in subsequent tracings. In this group, four children suffered from rheumatic fever and two suffered from hemorrhagic nephritis.

An S-T segment deviation greater than 2 mm. above or 1 mm. below the isoelectric line was considered abnormal.

A T wave greater than 8 mm. in amplitude in CF_2 or CF_4 or an inverted T wave greater than 8 mm. in Lead CF_2 or 6 mm. in Lead CF_4 was considered abnormal.

The presence of features in the electrocardiograms of normal children which would be interpreted as abnormal in adults necessitates the use of caution in the interpretation of a single electrocardiogram obtained from one or more precordial positions in childhood. However, after rheumatic fever children not infrequently show abnormal changes in the precordial leads which are not present in limb leads and these changes present an additional clue to the presence of myocardial damage.

BELLET.

The authors did not feel that there was any likelihood that rheumatic fever was responsible for the findings in these four patients. However, three of the four patients had an erythematous rash and joint pains. This suggests that the diagnosis of rheumatic fever may occasionally have to be eliminated in making a diagnosis of infectious mononucleosis.

MCMILLAN.

Ward, D. E., Jr., and Harrell, George T.: The Effect of Salicylate Therapy on the Weltmann Serum Coagulation Reaction and Its Use as a Prognostic Test in Rheumatic Fever. *Am. J. M. Sc.* 211: 157 (Feb.), 1946.

In addition to the leucocyte count, two laboratory tests are available for the estimation of the degree of activity and the prognosis of rheumatic fever: the sedimentation rate and the Weltmann reaction which is based upon the fact that calcium chloride coagulates blood serum. Since there is evidence that the sedimentation rate may be altered by salicylate therapy, the authors have studied the Weltmann reaction to determine whether it likewise is influenced by salicylates, and also to determine its sensitivity and usefulness in comparison with the sedimentation rate.

In normal serum the Weltmann coagulation band is always 6. While salicylate in concentrations much higher than those ever obtained in human subjects did shift the band to 7, the reaction was not affected by salicylate in anything like the concentration obtained under clinical conditions.

In the presence of active inflammatory change, the sedimentation rate increases and the coagulation band becomes lower. As activity lessens, the sedimentation rate lowers and the coagulation band shifts to the right toward the normal of 6. In untreated patients, the two reactions are generally but not always parallel. However, since the sedimentation rate is altered by salicylate, while the Weltmann reaction is not, the authors feel that the Weltmann reaction is a more reliable measure of activity.

MCMILLAN.

Lequime, J., van Heerswyngheles, J., and Herlant, M.: Contribution to the Study of Congenital Dilatation of the Pulmonary Artery. *Arch. d. mal. du cœur* 37: 7 (Jan.-Feb.), 1944.

Clinical observations and autopsy findings are reported in a case of a woman, aged 32 years, who presented the syndrome of large pulmonary artery and small aorta. The patient had been breathless on effort since infancy and had been cyanotic since the age of 6 years. Essential features of the physical examination were cyanosis, clubbing of the fingers, a systolic murmur at the cardiac apex, and a faint diastolic murmur at the sternal border in the third left intercostal space. Radiography revealed a small aortic knob, very large pulmonary conus, and enlargement of the left ventricle. The electrocardiogram showed right bundle branch block. On postmortem examination, the right and left ventricles and the right auricle were hypertrophied and dilated, the pulmonary artery was greatly widened, and the aorta was narrowed along its entire course. An opening in the interventricular septum was present, having the diameter of 1 fingerbreadth, and situated just below the mitral and tricuspid valves. A second opening was present in the interauricular septum having a diameter of 1 centimeter.

Studies prior to the onset of cardiac failure had shown that the arterial blood had an oxygen saturation of only 74 per cent. From this it was calculated that 37 per cent of the venous blood by-passed the lungs by way of the shunt. The presence of the veno-arterial shunt was also manifested by an arm-to-tongue circulation time of 12 seconds. It is pointed out that the veno-arterial shunt is a critical handicap, the absence of which permits the patient to tolerate much better the aortic and pulmonary defects.

LAPLACE.

Conte, W. E., McCammon, C. S., and Christie, A.: Congenital Defects Following Maternal Rubella. *Am. J. Dis. Child.* 70: 301 (Nov.-Dec.), 1945.

Evidence is presented which suggests that infection with rubella predisposes toward development of congenital anomalies. To date, 136 cases of congenital anomalies have been

The authors discuss the role of heparin in this disease and believe that it is of doubtful value except in special circumstances. A table is given for the correlation of penicillin serum levels with twenty-four-hour dose. They feel that it is advisable to maintain a serum level of penicillin at least four times as high as the amount required to inhibit the growth of the organism *in vitro*. If this information is not available, they recommend a trial of 500,000 units by this method daily for two to three weeks. If unsuccessful, recourse to an appropriately equipped laboratory becomes imperative. M. W. STROUD.

Scherlis, S.: The Recognition and Clinical Significance of Auricular Heart Sounds. *Ann. Int. Med.* 24: 254 (Feb.) 1946.

The author discusses the difference between presystolic "murmurs" and presystolic "sounds" confusion in this regard may lead to a mistaken diagnosis of heart disease. Auricular sounds are usually obscured by the normal first heart sound but may be heard as a low-pitched sound in diastole in cases of A-V dissociation. The mechanism by which the two parts of the auricular sound are produced is discussed. The first part can be heard more easily in children, while the second part is heard in some cases of heart block. Auricular sounds have been noted clinically in patients with hypertension, sickle cell anemia, hyperthyroidism, and Besnier-Boeck-Schaumann disease without evidence of cardiac disease. Split first sounds at the apex are usually of equal intensity while an auricular component is softer and lower pitched than the ventricular component.

The mechanism of the Austin-Flint murmur of aortic insufficiency is said to be due to blood regurgitating through a damaged aortic valve against the anterior mitral curtain and pushing it into the blood stream passing from auricle to ventricle. The presystolic murmur of mitral stenosis is dependent upon effective auricular contraction but may be present in fast auricular fibrillation due to a summation of the mid-diastolic murmur and the normal first sound with shortening of diastole.

The importance of the left lateral position of the body to bring out sounds is noted and the simultaneous use of electrocardiogram, stethogram, and jugular pulse is illustrated to clarify the discussion. M. W. STROUD.

Sensenbach, W., and Buie, R. M., Jr.: Persistent Ventricular Bigeminal Rhythm in Apparently Normal Hearts. *Am. J. M. Sc.* 211: 332 (March) 1946.

In a series of 33 patients presenting bigeminal rhythm, eight patients were observed in whom evidence of heart disease was lacking but who had frequent regularly occurring premature beats. Four of these patients presented evidence of advanced arteriosclerosis so that heart disease could not be entirely excluded. In the remaining cases, occasional short periods of bigeminal rhythm were present in two women in whom profound emotional factors were found to be operative.

The two remaining cases of persistent bigeminal rhythm were observed in a 12-year-old mentally deficient girl and in a 33-year-old woman with rheumatoid arthritis, associated with marked emotional disturbance related to the skeletal deformity and the incapacity caused by the arthritis.

The cause for the occasional occurrence of persistent bigeminal rhythm with apparently normal hearts is unknown. BELLET.

Starr, I., and Friedland, C. K.: On the Cause of the Respiratory Variation of the Ballistocardiogram, With a Note on Sinus Arrhythmia. *J. Clin. Investigation* 25: 53 (Jan.) 1946.

Ballistocardiographic impacts increase in size during inspiration and decrease in size during expiration. Evidence is presented showing that this variation is due to changes in pressure rather than to changes in the heart's position. It is impossible to reverse the respiratory effects upon the ballistocardiogram by changing the subject's position on the table. Inflation of the lungs by a blast of air is capable of reversing this respiratory variation even though the heart's axis is brought closer to the axis of the recording instrument by the

Rantz, A. L., Spink, W. W., and Boisvert, P. J.: Abnormalities in the Electrocardiogram Following Hemolytic Streptococcus Sore Throat. *Arch. Int. Med.* 77: 66 (Jan.), 1946.

Detailed serial electrocardiographic studies were made in 185 patients with acute hemolytic streptococcal disease of the respiratory tract, approximately 50 of whom exhibited signs of an arthritic or nonarthritic continuing disease. Definite electrocardiographic abnormalities were observed in 31 of these patients. Twenty-two patients belonged to the nonarthritic group. This group manifested significant prolongation of the P-R interval in 15 patients and T-wave changes in seven patients. The abnormalities persisted from three to twenty-eight days. Of the group of patients who had gonorrhea with arthritic manifestations, five showed conduction disturbances and four showed T-wave changes. Arthritic poststreptococcal disease was more severe than the nonarthritic type. The presence of these electrocardiographic changes was invariably associated with other evidence of a continuing abnormal tissue reaction, as manifested by elevated sedimentation rate, fever, malaise, or arthritis. The authors emphasize that the abnormalities of the electrocardiogram of the type observed in their study during the poststreptococcal state may also be observed during and after attacks of other infectious diseases, such as typhoid, typhus, gonococcal arthritis, pulmonary tuberculosis, malaria, rheumatoid arthritis, and lobar pneumonia. They suggest that the frequency, duration, and magnitude of the abnormality will be greater after an infection by hemolytic streptococci, but that true specificity of the changes observed cannot be established. It is concluded that the manifestations which follow acute hemolytic streptococcal infection of the respiratory tract are similar to those of rheumatic fever, that the type of poststreptococcal continuing disease with arthritis is a tissue reaction identical with that ordinarily described as rheumatic fever, and that the nonarthritic illness is a closely related process. BELLET.

Hartz, P. H., and Van der Sar, A.: Occurrence of Rheumatic Carditis in the Native Population of Curacao, Netherlands West Indies. *Arch. Path.* 41: 32 (Jan.) 1946.

There is a widely accepted belief that acute rheumatic fever and rheumatic carditis are extremely rare or actually nonexistent in the tropics. Opinion in this regard is unreliable, however, when it is based on clinical observation alone. Only when autopsies and careful histologic examinations have been made in relation to a known sample of the population can conclusions as to the incidence of these diseases be considered valid. In a controlled study, it was found that among 3,391 medical admissions to a hospital in Curacao, Netherlands West Indies, during a period of five years, there were 61 patients who had acute rheumatic fever and three patients who had chorea. No cases of scarlet fever were observed. Among 1,307 autopsies on natives of Curacao, Aruba, and Bonaire, typical gross lesions of rheumatic carditis were found in 20 cases. Histologic examination was made in 12 of these cases, and in 11 instances Aschoff lesions were identified.

Rheumatic fever is certainly more frequent in the tropics than is commonly believed. There is a need for more reliable data on the subject, especially for autopsy studies with histologic examination. LAPLACE.

Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin. *Ann. Int. Med.* 24: 170 (Feb.) 1946.

The authors present 15 new cases of subacute bacterial endocarditis treated with penicillin in addition to the follow-up of 17 of the 20 cases which they previously reported. Of the 35 patients, 30 are alive and apparently cured of the infection. The average period of follow-up has been fourteen months.

Their method of treatment consisted of continuous intramuscular drip for eight to twenty-seven days. A twenty-four-hour volume of 250 to 500 c.c. of penicillin solution in 0.85 per cent sodium chloride was well tolerated. Repeated courses were necessary in some cases, with increased dosage and/or length of time, depending on the sensitivity of the individual organisms to penicillin. No relapses occurred later than two weeks after treatment. In no case did the infecting organism develop significant resistance to penicillin. Two patients died but culture at post-mortem examination revealed no active infection.

Book Reviews

VALOR PRONOSTICO DEL ELECTROCARDIOGRAMA. By M. Vela, M.D., Libreria Edit., Cient. Med. Esp., Madrid, Spain, 1944. Vol. 1 contains 336 pages with 252 illustrations, and Vol. 2 contains statistical data.

This work deals with the prognostic value of electrocardiography, a fascinating but extremely difficult problem.

The first part is devoted to an historical review. The second discusses the material on which the writer's work is based, namely 11,000 ambulatory patients. The third part discusses the prognosis for each wave pattern and for each electrocardiographic diagnosis. The fourth part discusses the mode of death and the age at death in different diseases.

The work is based on the study of two different tables. One of them lists the frequency of each electrocardiographic sign in the different diseases and its respective mortality. The other lists the mortality of each disease without considering the electrocardiogram. A comparison is then made between the mortality of a disease and that of the same disease when a certain electrocardiographic abnormality is present.

The relatively short duration of life of the patients (43 per cent of patients with mitral stenosis died within three years) indicates that they were examined for the first time when the clinical course was well advanced, a fact which lessens the interest of some of the data.

Among the results of the study, the following deserve mention: (1) Bundle branch block has a very high mortality, 68 per cent. (2) Inversion of T in Leads I and II has a 60 per cent mortality; T-wave inversion in Leads II and III has only a 47 per cent mortality. (3) Inverted T₂ with right axis deviation has a mortality of 64 per cent; inverted T₂ with left axis deviation may be normal. Left axis deviation with upright T may be a serious abnormality. (4) Sudden death cannot be foreseen on the basis of electrocardiographic tracings. (5) Patients with a normal electrocardiogram have a better prognosis than otherwise, whatever the disease.

Some of these and other conclusions may seem unexpected. This is partly due to the fact that one cannot correlate the electrocardiographic abnormality with the other clinical data, and partly to the inherent weakness of all statistical studies: their dependence on the method and material employed.

A. LUISADA, M.D.

diaphragmatic descent thus produced. Breathing through an obstruction and thus exaggerating the pressure differences of the cycle without influencing the changes of the heart's position greatly increases the respiratory variation of impacts. In a patient with an aneurysm of the left ventricle it was demonstrated that the right ventricle's contribution to the ballistocardioqram is greater than that of the left ventricle during inspiration and is less than that of the left ventricle during expiration. These relationships can be reversed by inflating the lungs with a blast of air. It is apparent that blood is sucked into the chest during inspiration thus enhancing right ventricular filling; left ventricular filling is diminished during inspiration owing to the increased quantity of blood contained in the expanded lungs. During expiration less blood flows into the chest and right ventricular filling is accordingly reduced whereas left ventricular filling is enhanced by the blood being "squeezed" out of the pulmonary reservoir. Records of arterial pressure obtained by means of the Hamilton manometer support this thesis in that arterial pressure declines during inspiration and rises during expiration. Sinus arrhythmia is related to reduced right ventricular filling during expiration: the heart behaves as if it were waiting for the right ventricle to be filled before contracting.

FRIEDLAND.

Elkinton, J. R., Danowski, T. S., and Winkler, A. W.: Hemodynamic Changes in Salt Depletion and in Dehydration. *J. Clin. Investigation* 25: 120 (Jan.) 1946.

Acute salt depletion in dogs produces a shocklike state resembling traumatic shock. There is a reduction in cardiac output, plasma volume, circulating plasma protein, blood pressure, circulation rate, and extracellular fluid volume. Water-depleted animals that have a comparable diminution in extracellular fluid volume do not display peripheral vascular collapse although cardiac output, plasma volume, mean arterial pressure, and circulation rate may decline. The hemodynamic differences between salt and water depletion may be related to complete maintenance or very slight reduction in the circulating plasma protein in the latter. The importance of salt depletion as a precursor of the shocklike state in untraumatized animals is emphasized.

FRIEDLAND.

Wiggers, H. C., and Ingraham, R. C.: Hemorrhagic Shock: Definition and Criteria for Its Diagnosis. *J. Clin. Investigation* 25: 30 (Jan.) 1946.

Hemorrhagic shock was produced in dogs by rapid bleeding from a femoral artery until the mean arterial blood pressure fell to 40 mm. of mercury. This level was maintained for ninety minutes by additional bleeding as needed and all the blood withdrawn was reinfused at the end of this period. A classification for the shock thus produced is proposed: (1) simple hemorrhagic hypotensive state in which the blood loss does not exceed 40 per cent of the total blood volume and from which the animal usually recovers by means of his inherent compensatory regulatory mechanisms; (2) impending shock state where the blood loss exceeds 40 per cent of the total circulating blood volume and from which the animal may recover if it is infused with suitable agents; and (3) irreversible shock state from which the animal does not recover despite infusion of suitable agents. Five criteria for the adequate diagnosis of the irreversible shock state are proposed: (a) spontaneous arterial pressure decline below 40 to 45 mm. Hg despite attempts to restore the blood pressure to "standard" hypotensive level by means of infusions of saline or whole blood; (b) relative hemoconcentration during the hypotension period [an unfavorable prognosis is indicated when the plasma specific gravity declines to a static level within the first sixty minutes of the hypotensive period; an even more unfavorable prognosis is indicated should plasma specific gravity begin to rise (after the initial decline) before the termination of the ninety-minute hypotensive period]; (c) diarrhea and passage of blood-tinged fecal material following the termination of the ninety-minute hypotensive period; (d) postreinfusion heart rate of 150 beats per minute despite normal blood pressure, indicating a state of irreversible shock; and (e) postreinfusion blood or plasma specific gravity which is likely to be higher than the control value in the animals that die whereas in surviving animals it is likely to be less than the control value.

FRIEDLAND.

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ACTINOMYCES SEPTICUS FROM HUMAN ENDOCARDITIS

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THE microorganism concerned in the present study was obtained in pure culture on four occasions, Feb. 2, 7, 26, and 28, 1944, from the circulating blood of J. R., a patient whose case was reported by Mac Neal, Blevins and Duryee.¹ The patient was desperately ill and was believed to be suffering from bacterial endocarditis with vegetation on the mitral valve and multiple embolic lesions involving the skin, mucous membranes, and brain.

In the original cultures from the patient's blood the microbial growth was recognized after incubation at 37° C. for ninety-six hours. On the plates of agar mixed with the patient's blood the colony eventually attained a diameter of 2 millimeters. It remained dry and seemed to become more thin and flat with age. An entire colony could be picked up on the end of the needle. In the original bottles of broth inoculated with the patient's blood, the colonies appeared as granular balls at the bottom of the broth on the surface of the layer of sedimented corpuscles. These colonies could easily be removed entire by the use of a capillary tube. In subcultures on slants of blood agar enriched with dextrose the growth was luxuriant and creamy in consistency. Continued propagation on this medium was easy. Weekly transplantation was necessary at first, but, after two months, transplantation once a month proved to be quite adequate for maintenance. On meat-infusion agar the growth was dry, scant, and unpigmented. On Sabouraud's medium and on Löffler's serum, growth was likewise sparse and delicate. In dextrose broth and in neopeptone broth there was produced at the bottom of the tube a granular sediment which occasionally extended along the side wall of the tube. After prolonged cultivation on artificial media the sediment in these cultures tended to become smoother, and after cultivation for several months the organism grew as a heavy sediment

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Fig. 1.—*Actinomyces septicus* drawn to scale with the aid of Abbé camera lucida. Portions of two microscopic fields have been brought together for this illustration.

with slight general clouding of the supernatant broth in forty-eight hours. Pellicle formation was not observed. It would seem that the gradual adaptation to growth in these culture media had been associated with a tolerance of increased oxygen in the environmental medium, perhaps merely because of greater growth vigor. On potato, raw or cooked, the growth was scant and without pigmentation. The culture growth in gelatin at 37° C. for two weeks permitted the gelatin to congeal on cooling. Milk used as a culture medium was coagulated in twenty-four hours. Dextrose, saccharose, maltose and mannite were fermented with production of acid without gas. Lactose, salicin, raffinose and inulin were not fermented. A broth culture one week old heated at 75° C. for fifteen minutes could not be subcultured although the unheated control remained viable. No motility could be observed and no acid-fast elements could be found. In young cultures the filaments were in part gram-positive. After ninety-six hours in broth these filaments became predominantly gram-negative.

The inoculation of rabbits, guinea pigs and mice neither gave rise to gross lesions nor caused death. After intravenous injection of the culture into mice and rabbits, multiple microscopic nodes of consolidation with necrotic centers were observed in the lungs, but the microbes were not recovered from these nodes and the attempts to demonstrate their presence by staining sections of lung were not successful. It is probable, however, that diligent repetition of these experiments and the use of different time intervals after inoculation would permit recovery of the organisms in culture and their detection in the tissue sections. Our studies, so far, have shown merely production of microscopic nodules and the lack of actively invasive pathogenic properties for the small animals.

Although the production of pigment has not been observed with certainty in any culture, the later maintenance cultures on slants of blood agar have shown a pale pink tint which is still evident when the colony is removed and spread onto white paper. The tint is similar to that in the condensation liquid at the bottom of the blood agar slant and may possibly be due to imbibition of the blood pigment by the bacterial colony without alteration of the hemoglobin.

The morphologic appearance of the organism under the microscope is shown in Fig. 1, in which are represented portions of mycelial growth seen in two different microscopic fields. The preparation was made from a culture in neo-peptone dextrose broth enriched with aseptic fluid, developed for forty-eight hours at 37° C., smeared on slides, fixed by flame, and stained by Gram's method. There is a branching nonseptate filament which tends to produce a tangled interwoven meshwork. The individual thread is extremely variable in diameter. The fact that portions are very slender suggests that the substance of the thread possesses a ductile quality which permits it to become extremely tenuous. At variable intervals there are round, ovoid, olivary, or more elongated masses which retain the intense violet stain. These masses attain a transverse diameter of 1 to 1.5 microns and as a rule are sharply defined. The intermediate portions of the filament are gram-negative, but not uniformly so, for in places there are minute granules in the substance which retain the violet dye to a variable degree. As the culture becomes older, the gram-positive elements become relatively less

abundant and the gram-negative portions of the filament become relatively more conspicuous. The relation of the different types of substance in the filament and their biologic significance have not been fully elucidated. When stained with carbolfuchsin and decolorized with acids, the threads are bleached. No acid-fast portions have been found in young or in old cultures. Even after long cultivation on artificial media the mycelium tends to remain undivided. Individual bacillary and coccoid elements occur but they are not conspicuously abundant.

The behavior of this organism in the presence of anti-infectious agents is a matter of practical importance. After repeated transplantation to promote vigorous growth this organism was introduced into neopeptone buffered broth enriched with dextrose and aseptic fluid. An adequate inoculation produced abundant growth in twenty-four hours. A series of tubes was prepared containing this medium and progressively smaller amounts of penicillin. The first tube contained 50 Oxford units of penicillin in a total volume of 10 ml., representing 500 units per 100 ml.; the next contained a concentration representing 250 units per 100 milliliters. The concentrations in the remaining tubes represented 125, 63, 32, 16, 8, 4, 2, 1, and 0.5 units per 100 ml.; the last tube, a control, contained no penicillin. On February 28, a qualitative result indicated a definite inhibition of growth by penicillin, but growth of the organism was not vigorous enough for quantitative readings. On March 12 complete inhibition of macroscopic growth was observed through the series to and including the tube containing 1 unit in 100 ml. of medium, or 0.01 unit per milliliter. A parallel series of tubes inoculated with the staphylococcus (F.D.A. 209) showed complete inhibition in a dilution of 2 units per 100 ml., or 0.02 units per milliliter. After much longer cultivation of the actinomyces *in vitro* it was found that 4 units of penicillin per 100 ml. were required to inhibit macroscopic growth. This variation was evidently related to the acquired vigor of growth in culture media, which was quite pronounced with this microbe. Sodium bismuth thioglycollate (thiobismol), 1 mg. in 100 ml. of medium, was germicidal to this actinomyces; 0.1 mg. in 100 ml. caused inhibition of macroscopic growth and 0.01 mg. per 100 ml. caused slight inhibition of growth as compared with the control tube. This result was obtained with a vigorous culture on Sept. 12, 1944.

This organism may be placed with confidence in the order of Actinomycetales (Buchanan²) and perhaps with less certainty in the family Actinomycetaceae (Buchanan²). Generic classification within this family is still somewhat unsettled. The renewed interest in this group of microbes which has come about in part because of the search for biologic anti-infectious agents may bring advances in knowledge of the entire order which will permit a revision of the classification and nomenclature. Recently Waksman and Henrici³ have recognized two genera, chiefly on the basis of oxygen requirements for growth. *Actinomyces*, including strictly anaerobic organisms, and *Nocardia*, including the aerobic forms. Unfortunately some of the pathogenic types of these filamentous bacteria seem to be anaerobic or micro-aerophilic when recently taken from the body of the host, but are able to adapt themselves after a time so that

We^o have, therefore, tentatively designated this organism as *Actinomyces septicus*, nov. spec., pending further advances in the study of the entire biologic group.

SUMMARY

1. A branching filamentous organism was obtained on four occasions during February, 1944, in cultures of blood from a patient with bacterial endocarditis.
2. This organism exhibited the characteristics of a micro-aerophilic actinomyces, irregularly gram-positive and not acid-fast.
3. It was susceptible to the action of penicillin but became more resistant to this agent after prolonged cultivation *in vitro*.
4. Bacteria belonging to the Actinomycetaceae have been reported in cultures of the blood during life infrequently. The present microbe is evidently different from these.
5. The name *Actinomyces septicus*, nov. spec., has been tentatively suggested.

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vigorous growth in culture media takes place under either anaerobic or aerobic conditions. These authors have furthermore proposed a new family, Streptomycetaceae, to which some of these bacteria would be transferred. Pending further clarification of the matter, we would place our organism in the family Actinomyetales (Buchanan) and in the old genus *Actinomyces* (Harz, 1877) rather than in the new genus *Streptomyces* (Waksman and Henrici, 1943).

Specific designation presents even more difficulty. The many morphologic and physiologic features of organisms in this group require more study to ensure certainty as to constancy in a given instance and their reliability as a basis for recognition of valid species.

So far as we have been able to ascertain, there is no previously recorded example of the clinical disease observed in the patient J. R. There are records of generalized infection with filamentous bacteria, some of which seem to be closely related. In 1907 Löhlein⁴ observed at necropsy an individual with generalized streptotrichosis evidently originating in the respiratory tract and extending through the blood stream to invade all the viscera. Cultures of the blood during life were negative, including the one taken forty-eight hours before death. At the post-mortem examination two days after death an agar plate inoculated with only three drops of heart's blood yielded countless colonies of the filamentous microbe. This microbe was also found in the metastatic abscesses throughout the body and in the large primary abscess in the lung. The organism was partially acid-fast; it liquefied gelatin and produced yellow pigment. In 1925 Thjøtta and Gundersen⁵ reported isolation of a streptothrix from the blood of a patient with severe rheumatism. After incubation for two weeks the growth appeared as woolly colonies on the bottom of the culture flask and then extended along the wall to the surface, where it spread as a white, sealy pellicle. The authors thought that this streptothrix did not cause the disease.

Actinobacillus lignièresii (Brumpt) was obtained in blood culture during life from a patient who appeared to have endocarditis, first by Thompson and Willius⁶ and later, in the same patient, by Lawrence, Neuhauser, and Howell.⁷ This organism was classified in the order Actinomyetales and in the genus *Actinobacillus*. The growth in culture consists of gram-negative rods. The organism is obviously quite distinct from the filamentous organism in our patient.

Biggart⁸ found a filamentous organism in an abscess of the thigh and in the metastatic pyemic lesions throughout the body of a patient at necropsy. The microbe was aerobic and liquefied gelatin. The author recognized it as *Actinomyces graminis* (Bostrom). In some respects the organism from our patient resembles this. However, our organism is not adherent to the agar medium, does not liquefy gelatin, and has not produced pigment on potato, nutrient agar or Sabouraud's medium: it grows by preference beneath the surface of the medium as a micro-aerophil and may without question be accepted as pathogenic. The clinical features of the disease in which it has been recognized as the pathogenic agent have been so unique that they require some consideration in classification of the microbe.

J. R., a 39-year-old white man, born May 30, 1904, was admitted to the New York Post-Graduate Hospital on Feb. 26, 1944. His parents were born in Germany. His father died in 1920, and his mother is living and in good health. One brother, born in 1906, suffered a prolonged illness due to tuberculosis but is now in good condition.

Fig. 1.

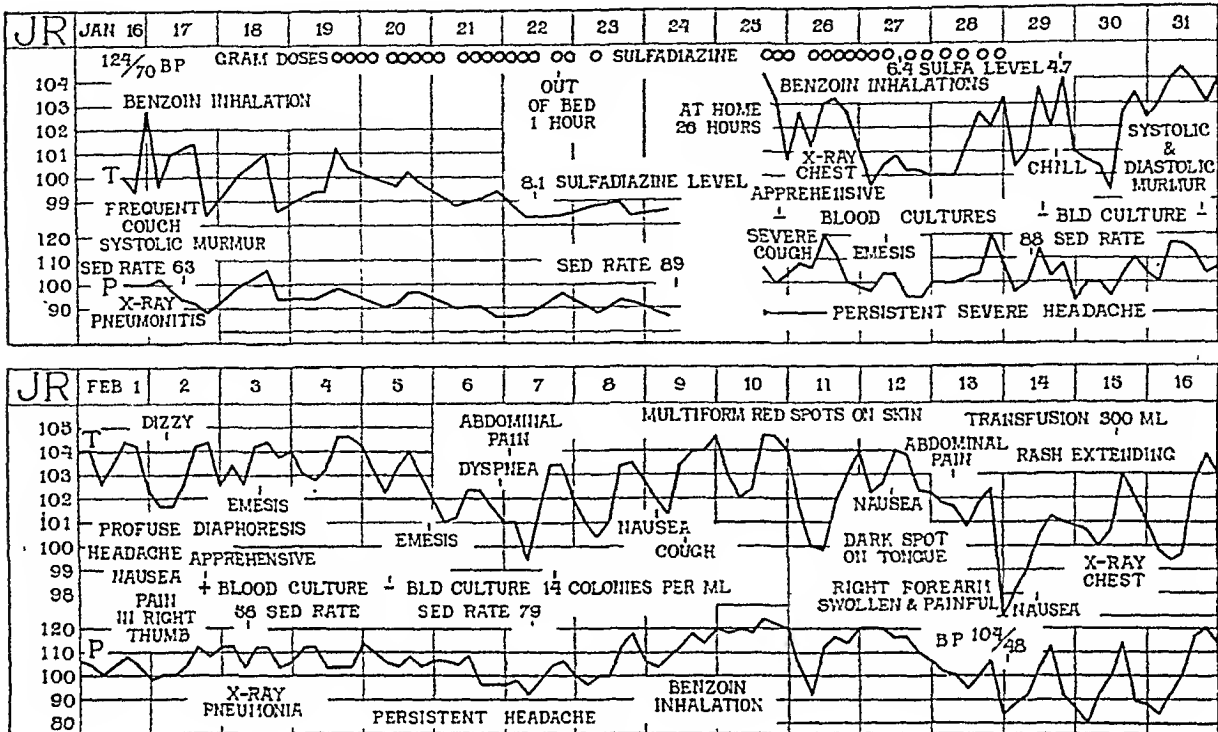


Fig. 2.

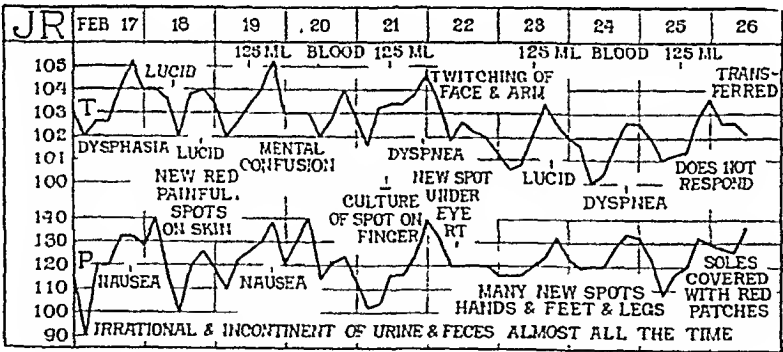


Fig. 3.

The patient was healthy as a child. At 11 years of age he had diphtheria and when he was 12 years old he suffered a severe respiratory infection while he was at a boys' camp in the summer. There was no swelling of the joints at this time. Subsequently he was subject to digestive upsets, ascribed to a "nervous" stomach. At 17 years of age he suffered a severe attack of malaria, which has not recurred. Early in 1932, when the patient was 28 years of age, a cardiac murmur was detected for the first time. He was advised to give up tennis in 1942 and in June, 1942, he was rejected for military service because of the heart murmur. He is a financial broker.

On Sept. 20, 1943, he and his wife went to Hollywood, Calif., for a three months' vacation. During this time he visited Palm Springs, San Francisco, and Arrowhead Inn, as well as a dude ranch. Travel was chiefly by automobile but train and plane were used

CLINICAL ARREST OF ENDOCARDIAL ACTINOMYCOSIS AFTER FORTY-FOUR MILLION UNITS OF PENICILLIN

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AMONG the many microbes which have been incriminated as causative agents in the bacterial types of human endocarditis, the filamentous bacteria commonly designated as actinomyces have received rather scant attention. Perry¹ in his monograph on bacterial endocarditis does not mention actinomyces. Thjøtta and Gundersen,² in 1925, reported isolating from the circulating blood of a patient a slowly developing filamentous organism which they placed in the genus *Cohnistreptothrix* in the family of the Actinomycetales. The patient survived a prolonged illness considered to be typical rheumatic fever, and the presence of the filamentous bacteria was regarded as merely incidental and harmless. Cornell and Shookhoff,³ in 1944, reported three examples of cardiac actinomyces, in each of which the infection evidently reached the heart by direct extension from adjacent structures such as the esophagus or the lung. These authors found reports of 68 cases of cardiac actinomyces in the literature, to which they added their own three, and, in a supplementary note, two more. In most of these cases, the infection involved the pericardium and myocardium by extension, but there were 19 pyemic infections. The endocardium was involved in approximately 18 cases, sometimes by extension through the myocardium. Among these 68 patients, recovery was observed in only one, the patient of Bigland and Sergeant,⁴ in whom an actinomycotic empyema involving the pericardium was treated successfully by thoracotomy.

A filamentous organism belonging in this general group was obtained by Custis, Halley, and Bacon⁵ in cultures of the circulating blood in a patient with mitral endocarditis later confirmed by necropsy. The organism which they found was classified as *Actinobacillus lignièresii*. Thompson⁶ had recognized this same organism in 1932 in blood cultures from a patient with endocarditis in whom spontaneous recovery was observed.

In the present communication we present the record of a man, aged 39 years, with apparent actinomyces of the mitral valve, repeatedly positive blood cultures, multiple embolic lesions, aphasia, right hemiplegia, amnesia for a long period, and eventual apparent recovery from the infection. It seems very probable that the recovery was related to the therapeutic program in this instance.

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Fig. 4.

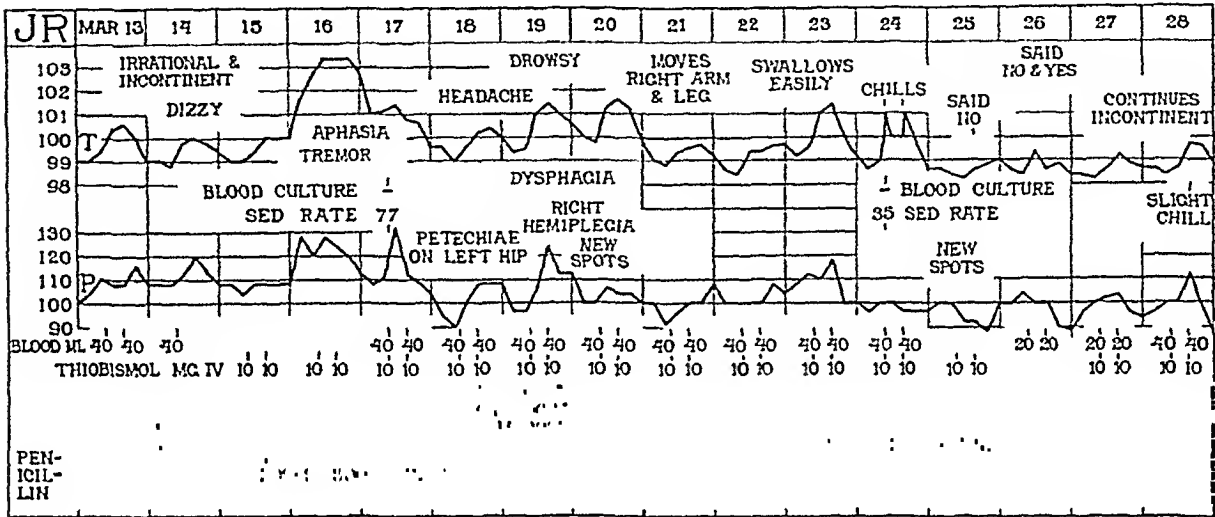
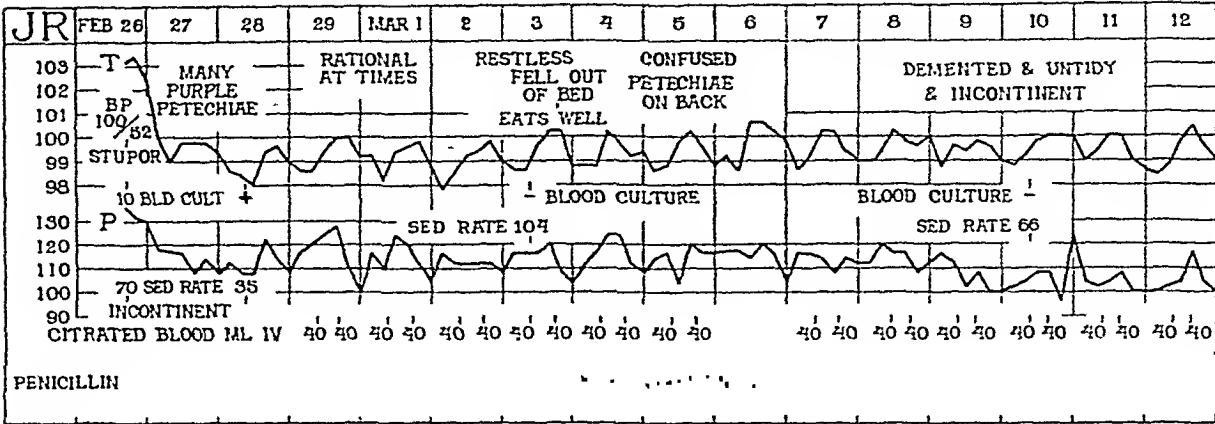


Fig. 5.

Fig. 6.

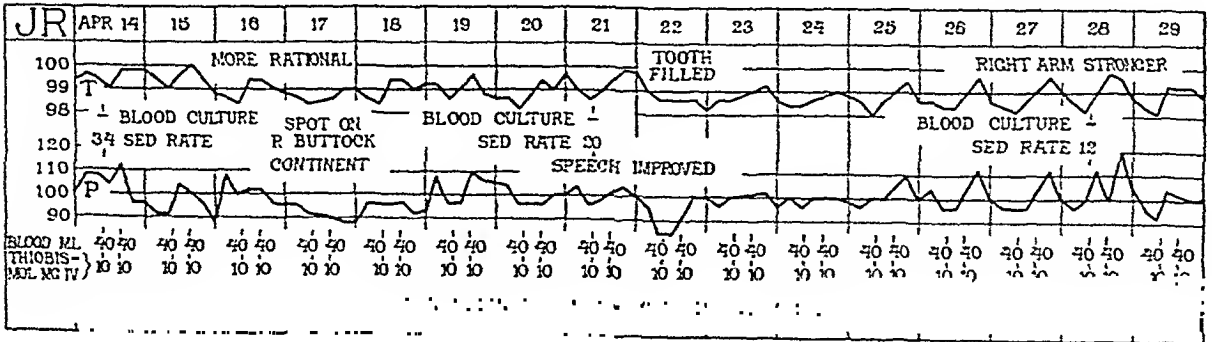
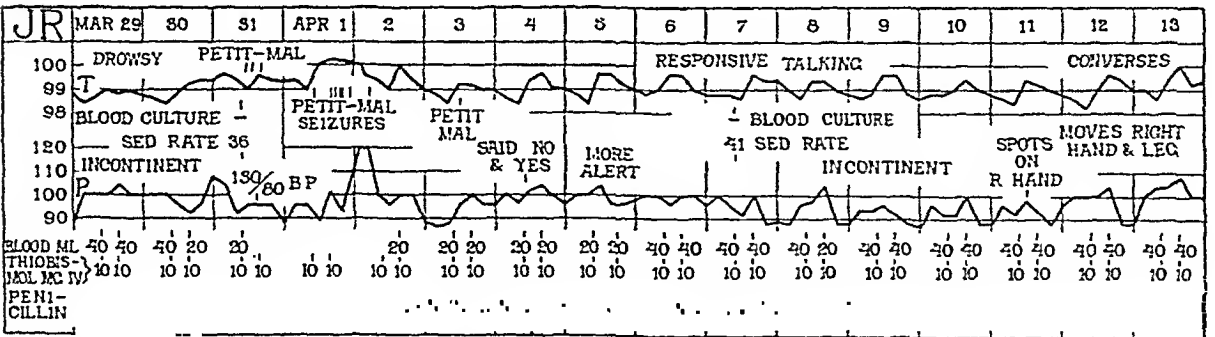


Fig. 7.

for the trip to San Francisco. He bathed in the ocean frequently. He remembers pulling up a long stem of grass along Hollywood Boulevard and chewing this stem for some minutes. He felt very well during the vacation until the last week, December 13 to 20, when he felt tired and below par. He and his wife left Hollywood by train on December 20. That night he felt feverish, omitted dinner, and remained in bed until they reached Chicago, on December 22. There he got some tablets at a drug store and had a good breakfast. He took an afternoon train which arrived in New York at 9 A.M. on December 23. He went by taxi cab to his apartment on 79th Street. On December 24, he went to his office and again on December 26 and 27, but thereafter remained in bed until December 31. On that evening he went out for dinner. However, he was forced to return home about 10 P.M. and call a physician (A. W. D.). On January 3, after two days in bed, the patient went to his office, but was sent home because he was obviously ill. That evening his temperature reached 104° F. The illness was considered to be a cold, and the physician was called again on January 10, at which time codeine and aspirin were prescribed. Four days later benzoin inhalations were started. A blood count on January 15 showed hemoglobin, 85 per cent; red cells, 4,200,000; white cells, 9,150; polymorphonuclear neutrophils, 73 per cent; lymphocytes, 25 per cent; mononuclears, 1 per cent; and eosinophils, 1 per cent. Of the neutrophils 9 per cent were band forms. A tentative diagnosis of virus pneumonia was made and hospitalization was arranged.

The patient was admitted to the Doctors' Hospital at 4 P.M. on Jan. 16, 1944. We are indebted to this hospital for access to the records which are summarized in Figs. 1, 2, and 3. By January 24 the patient seemed well enough to go home, where he promptly suffered a relapse. He was readmitted to the hospital on January 25. In addition to the cough, fever, and systolic murmur, the patient now had severe persistent headache, with occasional chills, nausea, and emesis. There was a change in the heart murmur. The fever could not be controlled, embolic lesions appeared, and cultures of the circulating blood made on February 2 and February 7 yielded a positive growth. There were 14 colonies per milliliter of the patient's blood in the culture taken on February 7. The microbe proved to be a branching filamentous actinomyces. After February 17 there were manifestations of increasingly severe intracranial deterioration until the patient became entirely unresponsive. On February 26, he was transferred to the New York Post-Graduate Hospital in a stuporous, unresponsive state. His temperature was 103.2° F., his pulse rate was 136, and his respiratory rate was 28. The diagnosis on admission was "vegetative endocarditis with widespread embolizations (including brain) and bacteremia." A specimen of blood showed a sedimentation rate of 70 mm. in 60 minutes, and its culture developed a growth of the actinomyces, 10 colonies per milliliter of the patient's blood. It was the general opinion that he would not survive the night. The intravenous injection of 5,000 units of penicillin every two hours was started at once.

Figs. 4 and 5 show the abbreviated record from February 26 to March 28. The fever showed a marked decline, but the mental derangement, with only occasional lucid intervals, persisted. On March 16 there was total loss of speech and, on March 19, complete right hemiplegia, complicated by difficulty in swallowing. There were also numerous new embolic spots on the mucous membranes and the skin. On March 20 the dose of penicillin was increased to 10,000 units every two hours. On March 21 he was able to move his extremities slightly, and on March 23 he was able to swallow without difficulty. He was able to say "No" on March 25 and both "No" and "Yes" on March 26. On February 28, two days after the initiation of penicillin therapy, the blood culture became positive, with less than one colony per milliliter of the patient's blood. All subsequent cultures of the blood remained negative; nevertheless embolic lesions continued to appear from time to time.

The abbreviated record from March 29 to April 29 is shown in Figs. 6 and 7. Here the length of the lines indicating doses of penicillin has been reduced to save space but the value of each dose is 10,000 units every two hours. From March 31 to April 3 there were repeated mild epileptic episodes. However, the patient recovered his speech and was able to converse, with some hesitation, by April 12. Embolic spots continued to appear from

Fig. 10.

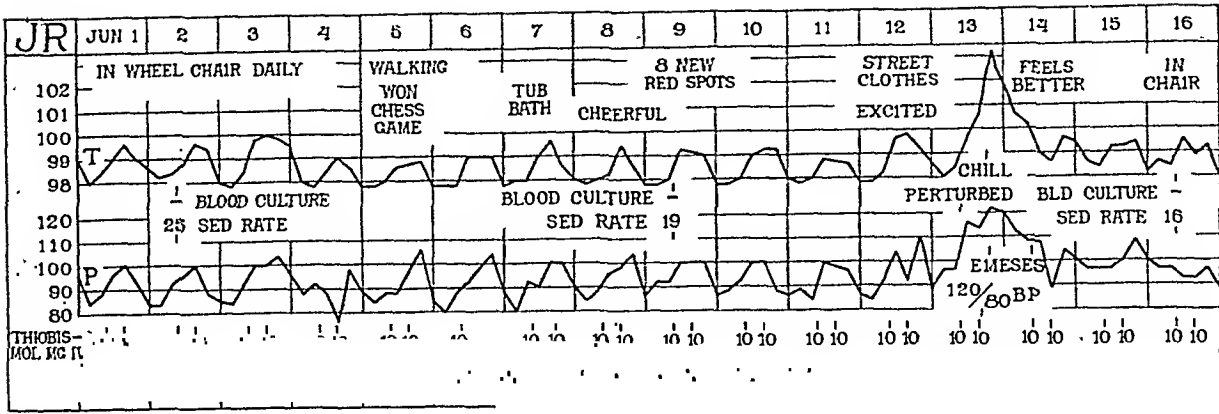


Fig. 11.

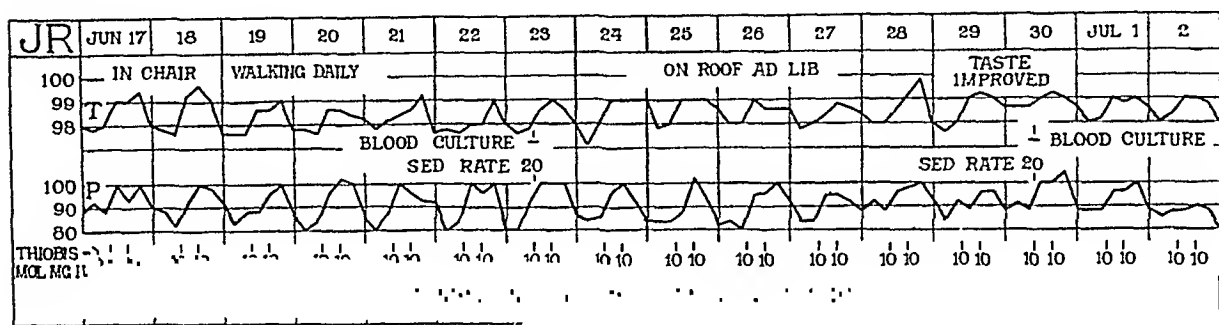


Fig. 12.

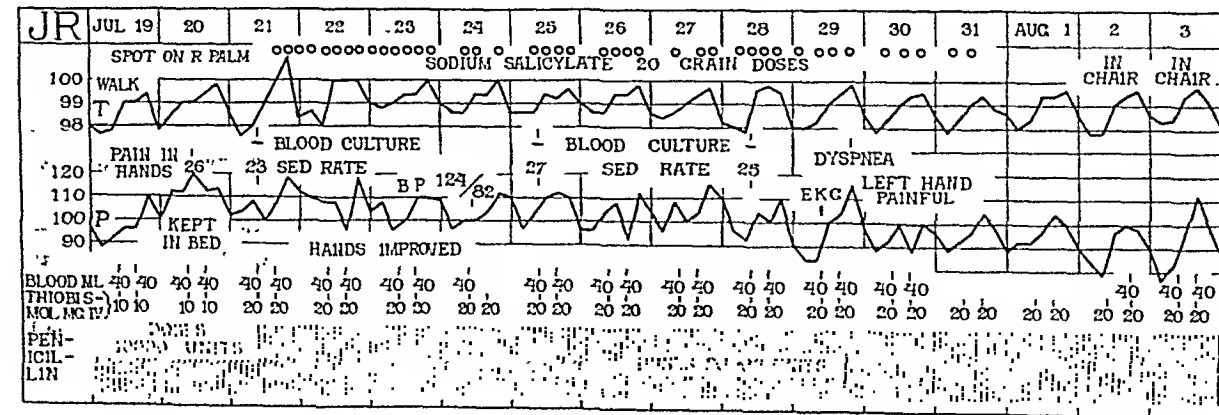
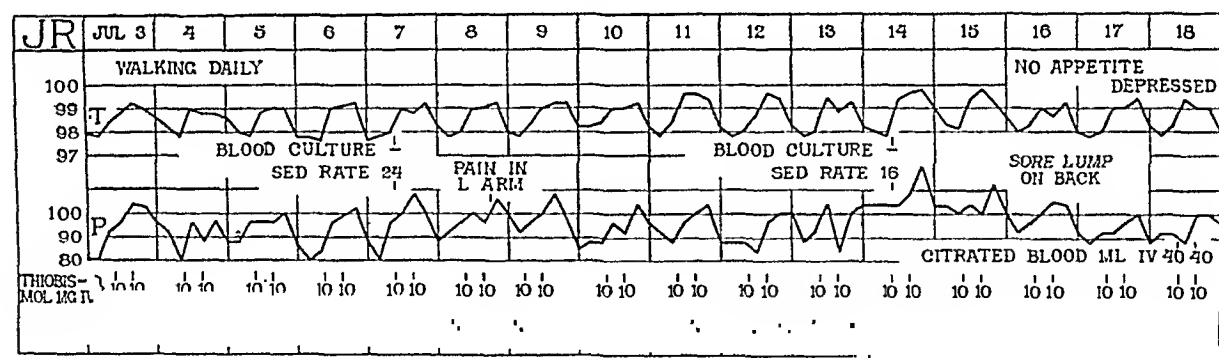


Fig. 13.

time to time. A tooth was filled on April 22. There was gradual return of strength in the right arm and leg.

The abbreviated record from April 30 to May 31 is shown in Figs. 8 and 9. Electrocardiographic examination on May 1 revealed left axis deviation and a sinus tachycardia with a rate of 105. The rise in temperature on May 3 was believed to be related to an emotional disturbance. By May 23 the patient was able to walk. On May 17 the dosage of penicillin was reduced to 5,000 units every two hours and on May 24 to 2,000 units every two hours. New painful embolic spots appeared on the left hand on May 28, and on May 30 there was a chill. The reduction of penicillin had been premature, although perhaps not to be too severely criticized when we recall the difficulties in penicillin distribution in May, 1944. On May 31, the dose was increased to 10,000 units every two hours. The patient remembers nothing from January 25 until about the middle of May.

Fig. 8.

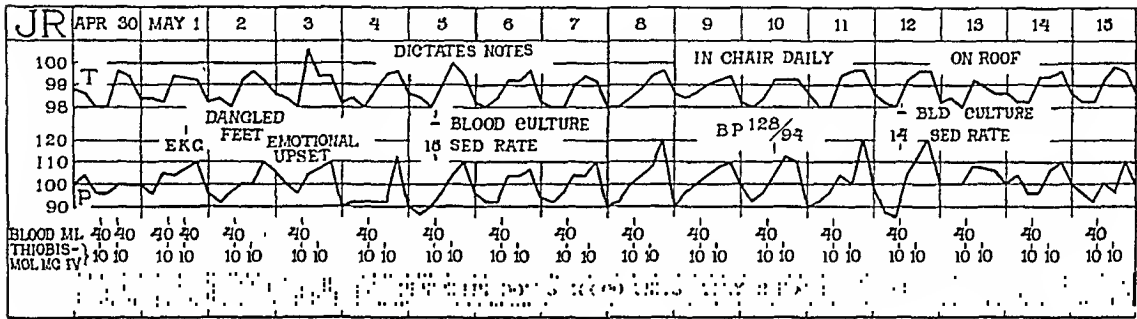


Fig. 9.

From June 1 to July 2 (Figs. 10 and 11) the clinical improvement continued and re-education progressed slowly. The patient played chess on June 5. There was another emotional disturbance on June 12 and 13, and the patient had a chill on June 13. By July 2 he seemed to be convalescent.

The record from July 3 to August 3 is shown in Figs. 12 and 13. The patient progressed very well until July 16, when there was a tender swelling in the back which appeared to be embolic in origin. Other embolic lesions appeared on July 19. Strict bed rest was again enforced. Sodium salicylate in doses of 20 grains every four hours was started on July 21 and was continued with some irregularity until July 31. On July 21 also the penicillin dose was increased to 20,000 units every two hours. An electrocardiographic examination on July 29 revealed no essential change from the examination on May 1. On August 2, the patient was allowed to sit in a chair.

In Figs. 14 and 15, showing the abbreviated record from August 4 to September 4, the lines for penicillin doses have again been shortened. These doses were continued at 20,000 units every two hours throughout this period. Embolic spots in the palms of the hands were observed again after August 10, and on August 15 and 18 there were chills and

these peaks was preceded by emesis on October 16. The disturbance was ascribed to possible impurities in a new lot of penicillin, which was not used after October 17. The sedimentation rate on October 13, 20, and 27 and on November 3 was 15, 9, 18, and 6 mm. per hour, respectively. Rest in the recumbent position was still strictly enforced.

During the period from November 8 to December 9 the temperature reached 99.6° F. only once, on December 5. The thiobismol was continued as before. The dosage of penicillin was continued at 20,000 units every two hours until 10:25 A.M. on November 17, then reduced to 10,000 units every two hours until 7:30 A.M. on November 19 and to 5,000 units every two hours until 3:30 P.M. on November 21, when it was discontinued entirely. There was an episode of *petit mal* on November 22. On and after November 25 the patient was allowed to sit in a chair. Walking was permitted daily after November 27. The sedimentation rate remained low.

The thiobismol was discontinued after December 9 and the patient was unrestricted except that he was required to avoid fatigue. His temperature reached 100° F. at noon on December 18 and 99.8° F. on December 28. His pulse rate and his blood pressure, which was observed twice daily, became less irregular after December 18. Electrocardiographic study on December 23 gave the same result as that in previous electrocardiograms, except that now there were premature ventricular contractions. During this period the patient was kept occupied by a program of re-education in speech and penmanship and he was obviously interested in the frequent measurements of blood pressure, palpation of abdomen, and auscultation of the thorax. He was finally discharged from the hospital on Dec. 27, 1944. There remained some facial asymmetry and also some difficulty in finding the right word, so that his speech was slow and hesitating. The loud systolic murmur persisted.

The patient was seen at intervals during the next month at the hospital and at his residence. He remained under the care of a trained nurse. His progress was slow and at times precarious. Early in February, however, he left for California in the care of the nurse. Since that time we have received several reports, some of them from the patient himself in his own handwriting. The remnants of speech difficulty, of facial asymmetry, and of weakness of the right arm and leg which still persist are recognized only by the careful attention of a trained observer. To his friends and social acquaintances the patient appears entirely well.

COMMENT

We have attempted to present in an objective fashion the record of a patient, J. R., who has survived a septic disease in which there seemed at first no possible excuse for optimism. The diagnosis of actinomycosis of the mitral valve has been accepted by the consultants who saw the patient in January, 1944. This diagnosis rests upon the clinical evidence of changing structure and function of the mitral valve; the repeated multiple embolic insults to the skin, mucous membranes, subcutaneous tissues, spleen, and brain; and the four positive cultures of the circulating blood, taken on February 2, 4, 26, and 28, which all yielded growth of a branching, filamentous microbe designated as *Actinomyces septicus*, nov. spec. Against this diagnosis may be urged the lack of direct inspection of the endocardium and the absence of a lethal termination of the infectious process.

Physicians who have observed the termination of an infection by administration of three or four doses of penicillin in a period of twenty-four hours may regard the injections of this agent every two hours from February 26 to November 21, a period of nearly nine months, as absurdly extravagant. We believe, however, that the therapeutic agents, penicillin and thiobismol, exerted in this instance only a bacteriostatic influence upon the infecting microbe

elevations of temperature. On August 18 the following note was recorded: "The occasional upsets, such as that of August 15, and the eurious spots on the skin, as well as the scattered firm lumps felt in the subcutaneous tissues from time to time, all suggest that there is still some aetinomycotic infection on the mitral valve. The therapy seems to hold this infection in cheek but without as yet permitting *complete healing*. It seems to me that the patient should be protected as far as possible from disturbing stimuli, emotional, mental, and physical. It is probably unwise to allow him to transact serious business over the telephone, and it might be well to consider strict bed rest with use of bedpan for several weeks. Unless healing does take place we shall sooner or later be confronted with a progressive infection which cannot be controlled by penicillin or bismuth or by both combined." This serious view of the situation was accepted by the consultants and by the family. More embolic spots appeared and there were temperature spikes and a chill late in August. In spite of the elinical evidence of occasional microbie invasion of the eirculating blood, all cultures of the blood, after the positive blood culture obtained on February 28, two days after admission to the Post-Graduate Hospital, remained negative.

Fig. 14.

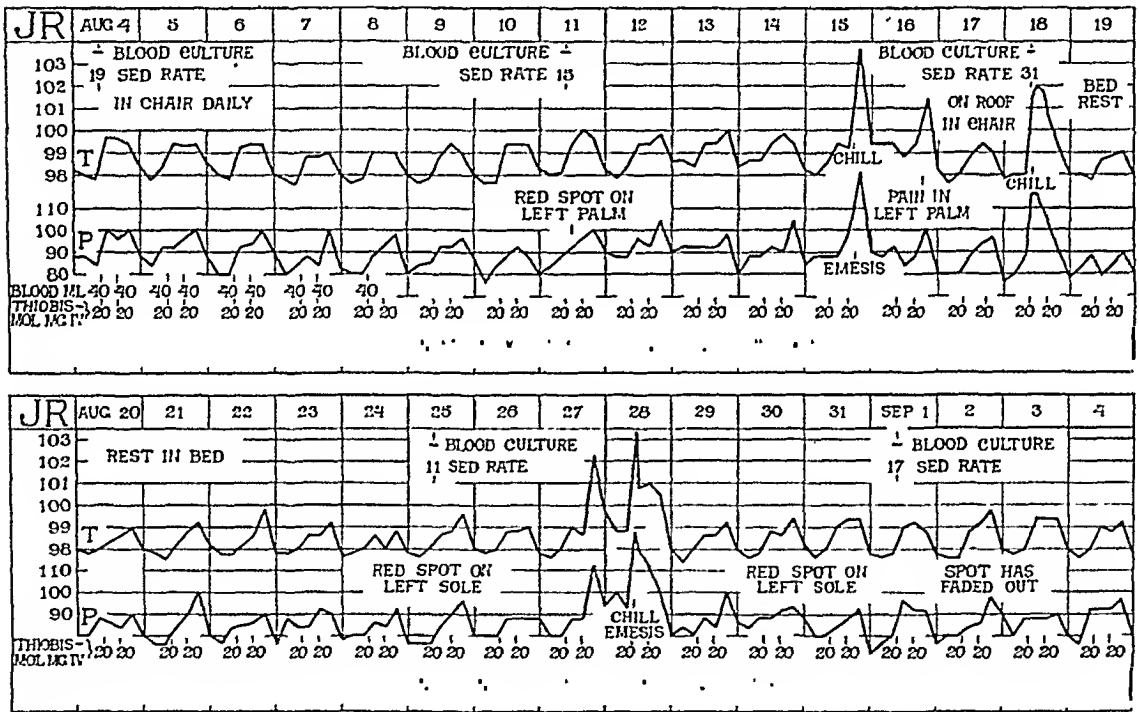


Fig. 15.

The charts showing the subsequent record are omitted because of the limitations of space. From September 5 to October 6 the thiobismol and penicillin were continued as before. Blood was not given during this time. The patient was not allowed to sit up but he was taken into the open air on a wheel stretcher on fair days. On September 16, new crowns were placed on two molar teeth. His temperature remained well below 100° F. except on one day, September 21, when it reached 100.4° F. in the afternoon. The pulse rate was 124 per minute, and there were twitching of the right faical muscles and increased difficulty in speech. These manifestations proved to be evaneseent.

From October 7 to November 7 the same therapeutic program was followed, and the elinical chart continued to indicate satisfactory progress. His temperature exceeded 99.4° F. on only two occasions; on October 17, when it reached 101° F. at noon, with a pulse rate of 140 per minute; and on November 2, when it reached 99.8° F. at noon. The first of

THE ELECTROCARDIOGRAPHIC EFFECTS OF INJURY AT THE ENDOCARDIAL SURFACE OF THE LEFT VENTRICLE

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FUNDAMENTAL postulates of modern electrocardiographic theory¹⁻³ may be extended for the purpose of predicting the form of electrocardiograms which might be expected from a subject having acute necrosis of the subendocardial laminae of the wall of the left ventricle.⁴ On the other hand, it is difficult to devise a practical experiment which will produce only a necrosis of these laminae without introducing factors which might complicate the interpretation of the associated electrocardiograms. The following case represents the occurrence of such a lesion which led ultimately to the patient's death.

A Negro woman, 44 years of age, was admitted to the Charity Hospital at New Orleans on May 1, 1944, with the chief complaint of severe burning pain in the chest. She had had shortness of breath on exertion since 1941. Two weeks before admission she experienced an attack of substernal pain which commenced shortly after dinner. The pain was attended by eructations, nausea, and vomiting, and a sense of smothering. The pain lasted one hour and did not radiate. A similar attack occurred later the same evening. Moreover, the attacks continued to recur daily throughout the next two weeks until the day of admission, at which time the pain had become continuous. With each attack the pain was of increased intensity and duration. On the day before admission the patient had developed dull, aching epigastric pain. There was no history of chills, fever, cough, or edema. Two years before the onset of her present illness, she had complained of moderately severe headaches and had been told by her doctor that she had high blood pressure.

Her temperature on admission was 94.4° F. The pulse rate was 140 per minute, and the respiratory rate was 20 per minute. Her physical development was good. She obviously was suffering from severe pain. No dyspnea was present and only one pillow was required for rest. The eye grounds showed tortuous arteries. No hemorrhages or exudates were present. The pupils were round, regular, and equal, and reacted to light and in accommodation. The cardiac apex impulse was felt in the left midclavicular line, was somewhat diffuse, and was of moderately increased force. The rhythm was regular. The heart sounds were loud and the pulmonary second sound was louder than the aortic. There was a moderately loud (Grade III) systolic murmur, with maximum intensity at the apex, which was transmitted throughout the left third and fourth intercostal spaces anteriorly. A high-pitched systolic squeak was also audible at the apex. The systolic blood pressure was 160, and the diastolic blood pressure was 105. The lung fields were clear. There were no additional noteworthy findings.

The patient required repeated injections of morphine sulfate (0.016 Gm.), which at times failed to give temporary relief. On the second day of hospitalization a severe attack of pain commenced suddenly. During the attack the heart rate was 140 per minute and the blood pressure was 160/104 in the right arm and 120/90 in the left arm. Moreover, subsequent observations showed rather unusual variations of blood pressure in one arm as com-

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and that healing had to progress by the slow processes of bacteriolysis, phagocytosis, encapsulation, and regenerative repair. The therapeutic program should doubtless be improved in future cases of this sort. Perhaps larger doses of penicillin would have been better. We now believe that the period of strict bed rest in the early months of the illness was terminated too soon in this case. However, at the time, most of the physicians were inclined to accede to the wishes of the patient and of his family, which are difficult to oppose when dealing with a chronic disease with so many unknown features.

The patient's condition has been reported as excellent in July, 1945, some sixteen months after the last positive blood culture was obtained (Feb. 28, 1944), and about eight months after termination of treatment with penicillin and thiobismol. We believe that the disease may properly be regarded as in a state of arrest. Concerning possible relapse no reliable opinion can be given at the present time. On March 1, 1946, the patient wrote to us to report himself in good condition.

SUMMARY

1. A man, aged 39 years, with clinical evidence of mitral endocarditis, complicated by right hemiplegia, aphasia and other signs of grave intracranial injury, and multiple peripheral embolic lesions, has shown so much improvement that the disease is now in a state of arrest.

2. Cultures of the blood yielded growth of an actinomyces.

3. The therapeutic program included rest in bed, sodium salicylate for a period of ten days in July, intravenous and intramuscular injections of penicillin, and intravenous injections of thiobismol and of citrated blood continued over a period of many months.

4. The total amount of penicillin injected was 43,972,000 units during the period from February 26 to November 21, and the penicillin actually expended, including waste and loss in handling, amounted to 50,010,000 units.

We are extremely grateful to Charles Pfizer and Company, Inc., of Brooklyn, New York, who supplied the penicillin from research allocations, under difficult conditions which will be appreciated by those physicians who attempted to employ this agent early in 1944.

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being relatively fresh and associated with almost no cellular reaction. Here the fibers are pink-staining and granular, and the nuclei are pyknotic.

"In other areas there are inflammatory cell infiltrations, in some cases consisting chiefly of polymorphonuclear leucocytes. In other places there are large vacuolated spaces where myocardial fibers are being dissolved by macrophages with swollen cytoplasm, as well as by polymorphonuclear leucocytes. In still other areas, the process seems to have been completed and there are now present in the myocardium small scars consisting mostly of fibroblasts with relatively small amounts of collagen material, and rather numerous macrophages filled with brown pigment. The medial coats of the medium-sized arteries are thickened by hyaline material or by an increase in the smooth muscle. A similar change extends into some of the smaller arterioles where hyalinization of the medial coat seems to be present. The large vessels contained in the section contain no thrombi.

"Sections of the left ventricle taken from approximately the midportion of the anterior wall show the endocardial layer of fibrous tissue to be very thin, and almost immediately beneath the endothelial cells the myocardium is extensively vacuolated and shows numerous macrophages with brown pigment in their cytoplasm. In some areas, most of the muscle tissue has disappeared, leaving fibrous tissue filled with brown pigment; but in general there is a layer of damaged, but not necrotic, muscle tissue immediately beneath the endocardium. Superficial to this layer there is a zone of necrotic tissue which is deeply pink-staining and in which many of the nuclei are gone. There are scattered blue-staining zones similar to those seen in the lower portion of the left ventricle. These necrotic zones do not extend entirely through the muscle coat as they did in the section previously described. They are limited to an area which lies closer to the endocardial than to the epicardial surface. In the layers of myocardium near the epicardial surface, there are small scarred areas extending about the blood vessels, and there is some separation of the muscle fibers from each other. In some areas there are a few polymorphonuclear leucocytes in the interstitial tissue, and in these regions isolated foci of muscle fibers are in the process of destruction. In general, however, the musculature seems preserved. The larger arteries show some thickening of their endothelial coats, and the change previously described is present in the muscular coats. The arterioles in some areas show a slight thickening of their medias which is produced by hyaline material."

Cubes of ventricular muscle with cauterized or sterile surfaces were macerated and cultured. The cultures showed no bacterial growth. The remainder of the necropsy findings were negative.

ELECTROCARDIOGRAMS

The electrocardiograms (Fig. 1), which were taken on the first, fourth, sixth, and tenth hospital days, show marked sinus tachycardia and downward displacement of the RS-T junction in limb Leads I and II and chest Lead IVF. It is observed that, if the axis of injury is plotted on the triaxial reference system according to the rule which defines its direction as that of a line drawn from the center of the left ventricle toward the center or centroid of the injured region,² a base-apex direction is determined which anticipates an upward displacement of the RS-T junctions in the limb leads similar to that of diffuse subepicardial injury of acute pericarditis. A diffuse injury of the subendocardial lamina is, however, the geometric inverse of that produced by acute pericarditis. Consequently, the effect of the former is an injury axis against-the-rule which has the direction of a line drawn from the center or centroid of the injured region toward the center of the involved ventricle. The mechanism involved has been referred to elsewhere⁴ as "injury-against-the-rule." The effect of injury-against-the-rule is produced whenever injury is greater at the endocardial than at the epicardial surface.

Comparison of the curves of Fig. 1 also reveals a progressive breakdown in the QRS complex. The breakdown is pronounced in Lead II and in Lead IVF. While QRS changes of this kind are not necessarily indicative of, they are usually evidence of, morphologic death of some regions of the ventricular wall. They are, in point of fact, indicative of electrical

pared with nearly simultaneous recordings from the other. Daily comparisons revealed a systolic difference of 40 or 50 mm., the high value appearing sometimes in one arm and sometimes in the other. Most of the remittent pain which occurred after hospitalization was confined to the epigastric region. On the sixth hospital day, gallop rhythm and a precordial friction rub were detected. The temperature ranged from normal to 100° F. during the first week, after which it leveled off and remained normal. On the eleventh hospital day, the patient suddenly lost consciousness, developed gasping respirations, and died within several minutes.

Urinalyses were negative. The red blood cells were normal. Repeated leucocyte counts were normal. The sedimentation rate was abnormally increased on repeated occasions. The blood and spinal fluid Kline and Kolmer reactions for syphilis were negative. A roentgenogram of the chest was normal.

Post-mortem examination of the heart showed moderate hypertrophy and dilatation of the left ventricle. The inner half of the wall of the left ventricle (including the interventricular septum) presented a soft brownish yellow necrosis. In the apical region the wall was relatively thin and firm and of slight grayish color due to early fibrosis. Elsewhere in the walls of the left and right ventricles were scattered areas of necrosis which varied in size from a few millimeters to 1.5 to 2 cm. in diameter. These foci were most numerous at the endocardial surface of the right ventricle. The endocardium proper, the valves, and the coronary arteries were intact.

Microscopic Findings.—*

“Sections from the right ventricle show the epicardial surface to be composed of loose connective tissue in which there are fat cells. Immediately beneath this layer the myocardial fibers are vacuolated, swollen, and pink-staining, and the nuclei are distorted. This muscle layer is not necrotic. Beneath this layer there is a varying picture which extends throughout the heart muscle. The pattern of this picture is irregular and does not seem to follow the distribution of any vascular supply. There are small areas where the muscle fibers are pink-staining and show pyknotic nuclei. These areas are interspersed with pale pink-staining zones where muscle fibers appear damaged but are not dead. In these areas, particularly in the former, there are zones where almost all of the muscle fibers have disappeared, and in their place are fibrous tissue stroma and macrophages. Some macrophages have distended cytoplasm with brown-staining granular material inside. A few polymorphonuclear leucocytes are present in these areas.

“In other areas there are blue-staining zones in which muscle tissue, as well as connective tissue stroma, has been disintegrated. In the blue zones, which are sharply circumscribed, there are many pyknotic nuclei and what appear to be colonies of bacteria. These areas are surrounded by relatively slight inflammatory cell reaction. At the periphery there are a few polymorphonuclear leucocytes, but the zone is not thick and the exudate is not marked.

“The endocardial surface is not well shown in the section, but where it does appear it shows alternating zones of necrotic and damaged muscle fibers extending to the endocardial surface.

“Sections of the left ventricle, taken from the lower portion of the anterior wall, show the endocardial surface somewhat thickened by edematous connective tissue infiltrated by polymorphonuclear leucocytes and mononuclear cells. The endocardial surface, however, is not covered by a layer of fibrin or thrombus. Beneath this layer there is a zone where the muscle tissue is vacuolated, the fibers are swollen, and the nuclei are distorted but not pyknotic. In some of the connective tissue septa which extend into this zone, there are infiltrations of polymorphonuclear leucocytes, presumably along the adventitia of blood vessels. Beneath this layer and extending through the entire wall of the heart to involve the epicardial surface as well as the underlying tissue there is the same type of patchy, necrotic lesion that was seen in the right myocardium. The necrotic lesions seem to vary considerably in age, some

*I am indebted to Dr. Edward L. Burns, of the Pathology Department of the Louisiana State University Medical School, for the microscopic findings.

malaise or leucocytosis. The low-grade fever and the increased sedimentation rate could be related directly to the myocardial necrosis. Certainly they are characteristic developments during the course of ordinary myocardial infarction. Indeed, if the electrocardiograms are not considered, the clinical picture is quite typical of that of repeated attacks of angina pectoris culminating in acute myocardial infarction. Moreover, the remarkable variations of blood pressure suggest a profound instability of the vasomotor system. On the other hand, the presence of essentially normal coronary arteries at post-mortem examination is by no means an assurance of normal physiologic activity of these arteries before death. The distribution of necrosis of the ventricular muscle is of a location which might be expected to occur as a result of a generalized coronary arterial spasm; that is, with a maximum intensity of necrosis in the direction of arterial irrigation or toward the apical and endocardial aspects of the ventricular walls. For those who hold that heart pain is an integral part of tension along the coronary arterial walls, a case of the kind under discussion would seem to require a pathologic physiology of the vasomotor activity of the coronary arteries. On the other hand, sudden death without pain or warning of any sort has been emphasized as a typical feature of diphtheritic myocardial necrosis. Studies on the intravenous action of pitressin, in which 90 per cent of the coronary flow is cut off by the drug, make it clear that a generalized coronary arterial shutdown is a physiologic possibility.⁷ Some such physiologic disturbance is presumed to occur in the brief, and at times fatal, attacks of angina pectoris in which, often enough, the coronary arteries are essentially normal in morphologic structure. In such cases, a disturbed vasomotor activity is generally assumed to be the basis for the occurrence, at times, of fatal ventricular fibrillation. The early advent of death in such instances precludes the development of the morphologic changes of myocardial necrosis which might otherwise indicate the distribution of ventricular ischemia associated with the spastic coronary state. Electrocardiograms are seldom recorded during fatal attacks of angina pectoris. On the other hand, electrocardiograms with final ventricular deflections which are like in kind (but less in magnitude) as compared with those recorded in the case under discussion, are obtained from the majority of patients suffering from a spontaneous or induced attack of angina pectoris, and also from normal subjects,⁸ where they have been ascribed to generalized ventricular ischemia. Modern theory dictates, however, that if a generalized ventricular ischemia were everywhere of uniform intensity there would be no associated changes in the form of the final ventricular deflections. For this reason, the decrease in the magnitude of the RS-T junction displacement observed in the last two curves of Fig. 1 is ascribed to a more nearly uniform distribution of injury (intense ischemia^{*}) at the epicardial and the endocardial surfaces of the ventricular walls.

From the standpoint of the electrocardiographic fundamentals, it is immaterial what view is taken as to the etiology of the myocardial necrosis in the

^{*}Electrocardiographic evidence of intense ischemia means that variety of RS-T junction displacement which is produced by a local gradient in intensity of polarization during diastole which temporarily reverses its direction during systole.

death of the intensely damaged regions. This interpretation, it will be observed, correlates satisfactorily with the autopsy findings.

DISCUSSION

Etiology.—The foregoing clinical picture and necropsy findings appear to conform to one of the varieties of acute isolated myocarditis.^{5, 6} The sterile cultures may indicate that a filterable virus was the etiological agent. It is unlikely that a toxic agent of infectious origin was present, for there was no discoverable infection from which such an agent might have spread. An auto-intoxication is meaningless unless it be understood to imply the effects of an abnormal hormone.

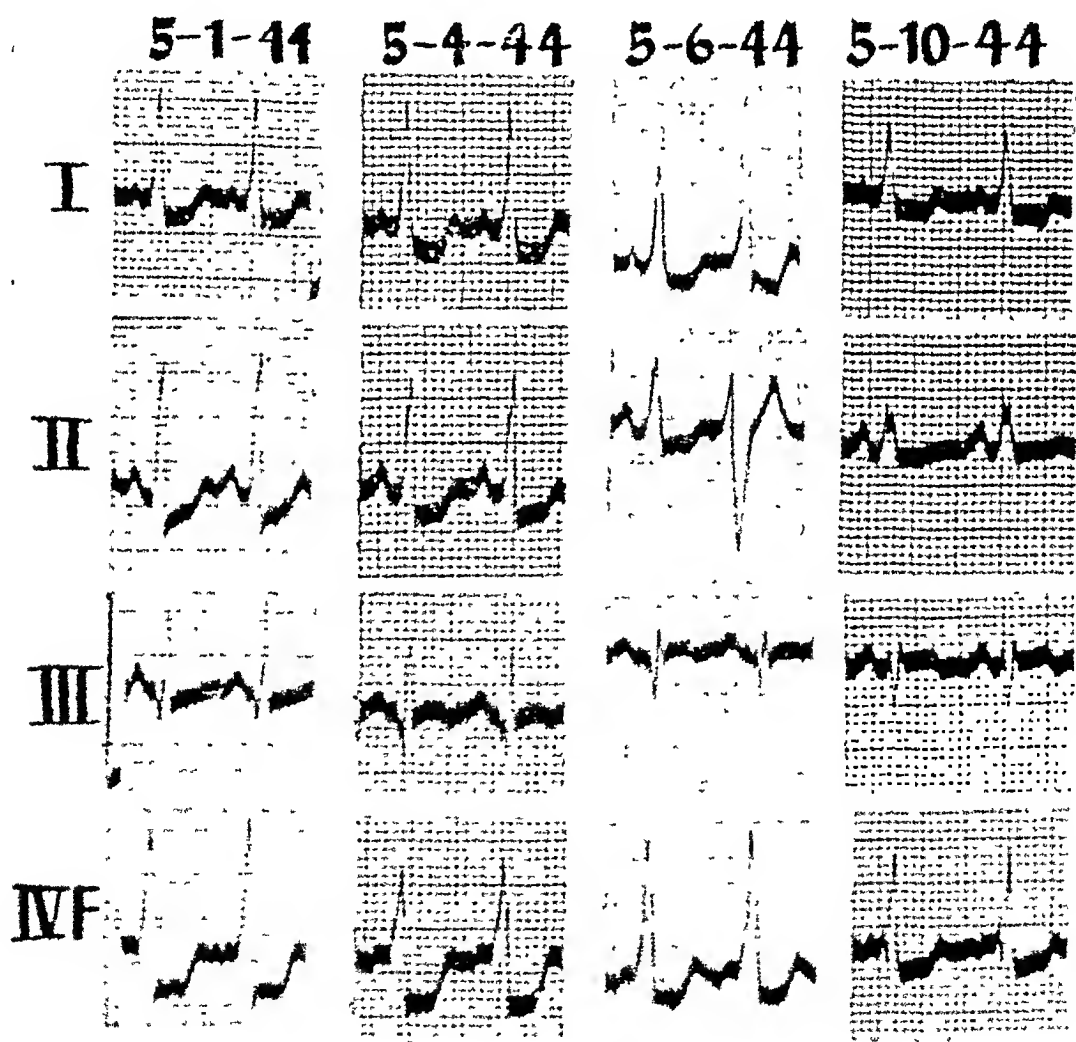


Fig. 1.—S-lead electrocardiograms which display the phenomenon of injury and distal effects of downward displacements of the RS-T junction in all limb leads and chest leads. Note the big S down of the QRS complex in the first chest lead and the ventricular extrasystole in the curve of May 6, 1944.

There is, however, another possible explanation, which is suggested simply because it appears sufficient. The clinical course was striking from the standpoint of absence of all definite evidence of infection. There was no general

"Case 6: The fresh infarct was extensive and involved the lateral portion of the left ventricle and extended somewhat posteriorly. This portion of the myocardium bulged. The infarct involved most of the wall of the ventricle but spared the Purkinje fibers. . . ."¹³

In general, it should prove rather difficult to correlate the electrocardiographic effects of injury with the morphologic changes in the myocardium. It seems highly probable that the three kinds of electrocardiographic changes (QRS, RS-T, and T) which have gradually become recognized as characteristic of myocardial damage are written by regions of the myocardium which present a normal morphologic appearance,¹⁴⁻¹⁶ the one exception being permanent QRS change.¹⁷ However, a region of recent morphologic damage is likely to define, between itself and physiologically normal muscle, a boundary within which lies the zone of critical physiologic activity that accounts for an abnormal electrical effect. Finally, it seems that injury-against-the-rule may occur in connection with: (1) the widespread myocardial necrosis of so-called isolated myocarditis, (2) acute myocardial infarction, presumably when the collateral circulation is poor, and (3) acute local ventricular ischemia of angina pectoris.

SUMMARY

1. A case is presented in which the distribution of myocardial necrosis is more extensive or intense at the endocardial surfaces and at the apex than at the epicardial surfaces of the ventricular muscle.

2. The electrocardiographic effects produced are in accord with the concepts of modern electrocardiographic theory.¹⁻³ The injury effects or RS-T junction displacements are the inverse of those which occur in connection with acute diffuse pericarditis. The mechanism has been described elsewhere as injury-against-the-rule.⁴ A unipolar lead recorded with the exploring electrode placed superjacent to the injured region displays a downward displacement of the RS-T junction when the intensity or extent of injury is greater at the endocardial, than at the epicardial, surface.

3. The phenomenon of injury-against-the-rule is observed in connection with certain cases of so-called isolated myocarditis, accounts for certain atypical electrocardiograms obtained from subjects with acute myocardial infarction, and appears to be a common feature of curves recorded from subjects undergoing an attack of angina pectoris.

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case under discussion. A distribution of necrosis which is more intense at the endocardial than at the epicardial aspects of the ventricular walls produces an injury effect against-the-rule. When a vector is drawn from the center or centroid of the injured region toward the center of the involved ventricle, it has the direction of a line which, when translated to the triaxial reference system, defines the direction of the RS-T junction displacements in all three of the limb leads of injury-against-the-rule. A precordial lead taken with the exploring electrode superjacent to an injured region of the kind under discussion will display a downward displacement of the RS-T junction. In connection with the application of these postulates to the interpretation of RS-T junction displacements which occur early during the course of myocardial infarction, the following excerpts are quoted from the author's correspondence with Dr. Harold Feil:

To Dr. Feil on May 24, 1944: "In the article" dealing with infarction of the lateral wall of the ventricle there are two cases (3 and 6) in which the injury shift is striking, particularly in Lead IVP. When the RS-T junction displacements of the limb leads are plotted on the triaxial reference system, they are found to be against, rather than with, the rule, that is, the vector which characterizes their effect is nearly the exact inverse of a directed line drawn from the center of the left ventricle toward the centroid of the damaged region, and Lead IVP in these cases further supports the idea that the net damage of the involved region is greater at the endocardial, than at the epicardial, surface.

"... The subendocardial arterial plexus of Gross¹⁰ is apparently a much more important factor in sustaining the subendocardial lamina of a region robbed of its natural blood supply than is inhibition or reversal of flow through thebesian veins. If this opinion is accepted, it may be observed further that survival of the subendocardial lamina (under an infarct) which accounts for injury-with-the-rule, depends largely upon an adequate collateral circulation at the time of the attack of infarction. Moreover, if an adequate collateral circulation is not available, the subendocardial lamina must, it seems, undergo necrosis along with the superjacent muscle, and the net result is a greater damage of the local subendocardial, than of the local subepicardial, laminae. In the event of a generalized coronary artery spasm, the plexus of Gross cannot operate effectively and the electrocardiographic pattern of injury-against-the-rule occurs as depicted in your article¹¹ of 1928.

"I am anxious to know if the subendocardial lamina of the damaged region in Cases 3 and 6 survived. It may be possible for you to give me information on the pathological material in these two cases. The analysis demands that the lamina in question did not survive, presumably because the plexus of Gross did not function."¹²

From Dr. Feil Oct. 18, 1944: "On looking over the pathological material of Cases 3 and 6, I have the following to report:

"Case 3: Sections of the myocardium revealed that the infarct involved the subendocardial muscle. The infarct did not extend through to the epicardium. . . .

ELECTROCARDIOGRAPHIC CHANGES IN ACUTE GLOMERULONEPHRITIS

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INTRODUCTION

IN 1789, Goodhart¹ reported that cardiac enlargement was not an infrequent complication of acute glomerulonephritis. Subsequent studies have noted the occurrence of congestive heart failure in from 17 to 71 per cent of patients with acute glomerulonephritis.²⁻⁸ Concomitantly, electrocardiographic abnormalities have been encountered in 60 to 100 per cent of the groups of patients studied.⁹⁻¹⁵ Various empirical abnormalities were observed in 43 per cent of our patients with acute glomerulonephritis. We previously reported that six of twelve patients with congestive heart failure showed clockwise rotation of the ventricular gradient suggesting that the myocardium of the left ventricle was acting as if it were ischemic.¹⁶

The present study represents an analysis of the electrocardiograms of 101 patients with acute glomerulonephritis. From the electrocardiograms, the electrical axis, the anatomic axis, the ventricular gradient, and the Q-T interval were computed, and the results were correlated statistically with the clinical findings in so far as possible.

In 90 of the 101 patients, a detailed analysis of the clinical and electrocardiographic findings was made. Half of the patients were white and half were Negroes; 61 per cent were men, and 39 per cent were women. Eighty-two per cent of the patients were 14 years of age or younger; the youngest was three months of age and the oldest was 34 years. A history of an upper respiratory infection preceding the date of onset of symptoms was obtained in 70 per cent of the patients. The only criterion applied in the selection of the patients for study was that one or more electrocardiograms had been taken. An average of 1.9 electrocardiograms were taken for each patient. Lead CF₄ was made in 96 of the 101 patients. In view of the fact that proper analysis of the relationships between the T wave and the QRS complex cannot be made without consideration of the ventricular gradient of Wilson, the analysis that will be described has been carried out. The method of the analysis is described in the appendix.

THE ELECTROCARDIOGRAPHIC CHANGES IN ACUTE GLOMERULONEPHRITIS

Deviation of \bar{G} .—The total series of 101 electrocardiograms in patients with acute glomerulonephritis was separated into three groups: (1) those showing an abnormal deviation of the gradient; (2) those which by every test were

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TABLE II. THE NORMAL DIRECTION OF THE VENTRICULAR GRADIENT OF SUPINE PERSONS IN RELATION TO THE DIRECTION OF THE ANATOMIC AXIS AND THE MAGNITUDE, A_{QRS}

THE OBSERVED ANGLE BETWEEN \hat{A}_{QRS} AND \hat{H}	THE AREA, A_{QRS} , IN 4 MICROVOLT-SECOND UNITS										
	1	2	3	4	5	6	7	8	9	10	11
0-4	0	0	0	0	0	1	1	1	1	1	2
5-9	0	1	2	3	3	4	4	5	5	6	6
10-14	1	2	3	4	5	6	7	8	8	9	9
15-19	1	3	5	7	8	9	10	11	12	13	14
20-24	2	4	6	9	10	12	13	14	15	17	19
25-29	3	6	8	10	12	14	15	16	18	20	23
30-34	4	7	10	12	14	16	18	20	22	24	27
35-39	4	8	12	14	17	19	21	23	25	27	31
40-44	5	9	13	16	18	21	23	25	28	30	33
45-49	5	10	14	18	21	24	26	28	31	33	36
50-54	6	11	16	19	23	26	28	31	33	36	39
55-59	7	12	17	21	25	28	31	34	37	39	42
60-64	7	13	19	23	27	30	33	36	39	42	46
65-69	7	14	20	25	29	32	35	38	42	45	49
70-74	8	15	21	26	31	34	37	41	44	48	51
75-79	8	15	22	28	33	36	39	43	47	50	53
80-84	9	16	23	30	35	38	41	45	49	53	55
85-90	9	17	24	32	37	40	43	47	52	55	57

difference between the means. The inclusion of a few adults in this series could hardly have modified the results.

The Magnitude of the Mean Manifest QRS Axis.—In the series of 78 normal children, A_{QRS} (see Appendix) was 4.12 ± 0.15 unit; in the whole series of 101 patients with nephritis, the value was 2.46 ± 0.13 unit. In this case the difference from the normal series is highly significant statistically. The inclusion of the adults with nephritis should lessen and not exaggerate the difference. A_{QRS} was smaller in Group 1 than in Group 2, but the difference was not certainly significant. The reason for the reduction in the net QRS areas in these patients is uncertain. In part, it may be associated with edema. It may also be due to a change in cardiac position, so that $\hat{S}\hat{A}_{QRS}$ had a more backward direction in the thorax; or it may be associated with the cardiac dilatation.

The Magnitude of the Ventricular Gradient.—In the electrocardiographically normal Group 2, G was 9.17 ± 0.31 unit. This is smaller than the normal children's mean of 11.60 ± 0.28 unit, and the difference is significant. The percentage decrease from the normal in this group, both in A_{QRS} and in G is almost the same; this suggests that the decreases are, at least in large part, brought about by the same factors. The standard deviation is 3.36 ± 0.22 unit. In Group 1, G was equally reduced, but the range is so great that nothing significant is to be learned from the figures.

The Direction of the Mean QRS Axis.—Both in the normal and in this series a single \hat{A}_{QRS} was omitted because its direction lay far outside the usual range. The average direction of the mean QRS axis (\hat{A}_{QRS}) in the normal series was $+61.10 \pm 1.58^\circ$; the standard deviation was $20.50 \pm 1.12^\circ$. The range, at three standard deviations, is -0.4° to $+128.1^\circ$. In the total nephritic group, the mean is not significantly different, though the standard deviation is greater. The difference in the standard deviations can hardly be regarded as significant, although occasional deviation of the QRS to the right in the nephritic patients is suggested.

within normal limits; and (3) those with an often normal \bar{G} (see Appendix), but with other abnormalities. In these three groups there were 42, 54, and five cases, respectively.

In Group 1 the gradient in 41 of the 42 patients was deviated to the right by 13 or more degrees; the range was 13 to 95°. The mean deviation was $33.10 \pm 2.30^\circ$ to the right of the normal as estimated from Table II. However, since the mean position of \bar{G} in a normal series of 78 children (including some with tachycardia) was $4.54 \pm 0.48^\circ$ to the left of the direction estimated from Table II, the actual mean deviation of \bar{G} in this nephritic group was closer to 37°. In calculating this mean, one case was omitted. In this single case, which in other respects differed from the others, \bar{G} was deviated 51° to the left, and not to the right. Since this is the single example of clearly abnormal leftward deviation, it is likely that it was due either to secondary effects of the disease or to some other associated defect. If the gradient is appreciably affected at all, the deviation is certainly nearly always to the right. This is associated with decreased height or inversion of the T wave in Lead I and usually with an elevation of the T waves in Lead III.

In Group 2, in which the electrocardiograms were empirically normal, the mean deviation of \bar{G} was $1.70 \pm 0.73^\circ$ to the left of the estimated position. This may be compared with the mean for the normal children. The difference between the means in the normal and nephritic patients is 2.8 ± 0.87 . The difference, being 3.2 times its probable error, can be regarded as probably significant, and suggests that some of the gradients, even in this electrocardiographically normal group, had actually been deviated a few degrees. In normal children the standard deviation was $6.21 \pm 0.34^\circ$, whereas in this series of nephritic children it was $8.15 \pm 0.51^\circ$. The difference is 1.94 ± 0.61 , again 3.2 times its probable error, and only probably significant. Yet this finding of greater scattering of values, almost entirely to the right, supports the conclusion suggested by the

TABLE I

EMPIRICAL ABNORMALITIES NOTED IN THE ECG'S OF 101 PATIENTS WITH ACUTE GLOMERULONEPHRITIS	NUMBER OF ECG'S SHOWING ABNORMALITY	
	ALONE	COMBINED
Diphasic or negative T_1	0	24
Negative T_1	23	
Relatively low T_1	20	
Low T waves	5	
Negative T_2	0	3
Negative T_2, T_3	1	
Prominent U waves	8	
Q-T prolonged	19	
P-R interval upper limits of normal for age and heart rate (Ashman and Hull)	4	
QRS changes suggesting left ventricular hypertrophy	1	
QRS changes suggesting right ventricular hypertrophy	1	
QRS widening, slurring, or notching suggesting intraventricular conduction defect	1	
Sinus tachycardia*	17	
Sinus bradycardia	8	
Partial right bundle branch block	1	
Other abnormalities in rhythm	0	

*Over 115 per minute in younger children; over 110 in older children; over 100 in adults.

Differences between the two groups were insignificant with regard to edema, weight loss, blood urea, size of the liver, pulmonary congestion, and the levels of the venous pressure and circulation time.

By the chi-square test the odds were six to one that the blood pressure would be higher among those patients with rightward deviation of \bar{G} than among those patients showing no electrocardiographic abnormalities.

Teleroentgenograms were obtained in 26 of the patients with normal \bar{G} and in 22 of those with rightward deviations. Cardiac enlargement was demonstrated in 17 of the former and 21 of the latter. The probability that cardiac enlargement was more frequent in patients with an abnormal \bar{G} was 90:1. If we include in the analysis those patients showing clinical evidence of cardiac enlargement we find that 24 of 50 patients with a normal \bar{G} and 37 of 40 patients with rightward deviation of \bar{G} had some evidence of enlargement of the heart. Chi for these data was 4.55 indicating that the probability that the differences between the two groups could be due to chance was but one in 300,000 plus. Thus 67 per cent of the 90 patients with acute glomerulonephritis showed clinical (25 per cent) or roentgenologic (42 per cent) evidence of cardiac enlargement, but this evidence was present in 92.5 per cent of those patients with rightward deviation of \bar{G} and in only 48 per cent of those with normal \bar{G} 's. We believe that these differences are statistically highly significant and suggest that cardiac dilatation may account, in part at least, for the electrocardiographic abnormalities in \bar{G} .

Empirical Abnormalities Observed in the Electrocardiograms.—In Table I are listed the number and kind of empirical abnormalities detected in the electrocardiograms secured from our 101 patients. A diphasic or negative T_4 was seen 24 times, a diphasic or negative T_1 was seen 23 times, a relatively low T_1 was seen 20 times, and low T waves in all limb leads were seen five times. Only rarely was T_4 abnormal in the absence of other electrocardiographic changes. These are the most frequent deviations from normal reported in the literature.⁹⁻¹⁵ Three patients had a negative T_2 in addition to a negative T_1 . The P-R interval was at the upper limit of normal three times and definitely prolonged but once according to the normal limits for age and heart rate established by Ashman and Hull.¹⁹ A higher incidence of P-wave and P-R abnormalities have been reported by Master^{10, 11} and Williams.¹⁵ An abnormally negative T_2 or T_3 was seen only once and significantly great QRS changes (widening, slurring, or notching), suggesting an intraventricular conduction defect, but once. QRS changes suggesting left or right ventricular hypertrophy were seen twice, each type being represented once. Sinus tachycardia was noted in 17 cases and sinus bradycardia was noted in eight, but no other abnormalities in rhythm were encountered. Sinus arrhythmia was often present. A partial and intermittent right bundle branch block was seen once. Prominent U waves were observed in eight tracings.

COMMENT

Langendorf and Pick¹² and Rubin and Rapoport⁷ emphasize the frequency of a low or negative T_1 associated with reciprocal increase in the voltage

The Relationship Between Heart Rate and the Magnitude of the Gradient.—

The magnitude of the gradient, G , varies inversely as the heart rate and directly with the magnitude, A_{QRS} . Before correcting for the latter factor, the abnormal series (Group 2) showed a fair correlation between heart rate and G . The coefficient was 0.493 ± 0.112 , which is just significant. In the electrocardiographically normal Group 1, however, no significant correlation was found. After correcting rate and A_{QRS} for age, Group 1 was unchanged, whereas the coefficient in Group 2 became 0.433 ± 0.100 , which is very probably significant. The total of these groups, after adjustment, gave a coefficient of 0.471 ± 0.075 , which is quite significant. It is of theoretical interest that the response of the gradient to rate changes in glomerulonephritis, when the electrocardiogram is abnormal, is like that in the normal heart.

The Q-T Interval.—The duration of the Q-T interval was expressed in terms of the constant, K , in the empirical formula: $Q-T = K \log [10(c + 0.07)]$, in which c is the cycle length and in which 0.07 is also a constant.²⁷ In Group 2, which exhibited gradient changes, the mean value of K was 0.419 ± 0.0029 , and the standard deviation was 0.0273 ± 0.0021 . In Group 1, the mean value of K was 0.399 ± 0.0022 , and the standard deviation was 0.0235 ± 0.0015 . In contrast, the mean K in the normal children was 0.393 ± 0.0011 , and the standard deviation was 0.0134 ± 0.00075 . The much larger standard deviation reflects the much greater range in Q-T interval duration in patients with glomerulonephritis than in the normal persons. The earlier report found a mean K value of 0.375 in children. The significantly greater mean in the present series of normal children probably reflects, in part, a present tendency to estimate these intervals as longer, and our later measurements of adults are in close agreement with Shipley and Hallaran.^{28*} If we place the upper limit of the normal Q-T at 2.58 standard deviations, then none of the normal series of children exceeds this figure; whereas it is exceeded by 14 of the nephritic patients in Group 1, and by three patients in Group 2. Two of the three latter patients had gradient deviations at 10° to the right. Upon return of the blood pressure and electrocardiogram to normal, the Q-T interval became shorter in the great majority of cases in which the later electrocardiogram was taken.

CORRELATIONS BETWEEN THE CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS

For analysis the patients were divided into two groups according to the deviation from normal of the ventricular gradient. In only 90 patients were both the clinical findings and the electrocardiogram available. In 50 patients the ventricular gradient was within normal limits and in 40, G was deviated 12° or more to the right (clockwise). Chi-square was calculated for the two groups in an attempt to correlate electrocardiographic changes with abnormalities observed in the blood pressure, the degree of edema, the amount of weight loss, the presence of clinical or roentgenographic evidence of cardiac enlargement, the level of the blood urea, and, in a few instances, for the values of the venous pressure or circulation time.†

*Since the timers of the electrocardiographs had not recently been checked, the discrepancy may have been due to this. Too rapid a timer will make the Q-T appear to be longer. This does not affect our conclusion.

†Hypertension was found to be present at some time in 86 of the 90 patients studied and abnormal urinary findings were, of course, present in all of the patients.

plain the absence of such cases in our series. It is possible that if pre-existing coronary disease is present, the predominant effects of an ischemic type of involvement will effect the part of the muscle supplied by the affected vessel.

The signs of left-sided failure are considered to be more frequent than those of right-sided failure, and when the latter is present there is usually evidence of concomitant left-sided failure. With cardiac dilatation, rightward deviation of \bar{G} is more commonly encountered, and this can be interpreted physiologically by stating that part of the myocardium of the free wall of the left ventricle is acting as if it were ischemic.

It has been reported by others that it was not uncommon for the electrocardiogram to be normal during the acute phase of acute glomerulonephritis and for changes to appear in the tracing when clinical improvement had become evident and the blood pressure was approaching normal. The importance of dilatation of the heart in the production of the electrocardiographic abnormalities can be evaluated only by the taking of serial tracings and teleroentgenograms. However, the correlation observed between the electrocardiographic changes and the presence or absence of cardiac dilatation suggests that the degree and duration of the increase in heart size bear an important relation to the abnormalities observed in the electrocardiogram of the patient with acute glomerulonephritis.

In almost every instance where frequent serial tracings were taken over a period of three days to three months, the abnormal electrocardiograms reverted to normal. However, changes in the electrocardiogram sometimes persisted for days after the patient was clinically well, a fact we cannot explain with the data at hand, but which is analogous to persistent T-wave changes which have been seen after the termination of a paroxysm of tachycardia.

Pathogenesis of the Gradient Changes.—It is likely that a combination of hypertension of rapid onset and cardiac dilatation produces the gradient changes observed in acute glomerulonephritis. When the hypertension is chronic, as in essential hypertension, the gradient is not usually deviated, and the following figures may be of interest. In 47 cases of hyperpiesia, in which the electrocardiogram revealed no clear evidence of left ventricular hypertrophy, the gradient was within the normal range in 40, deviated abnormally to the right in four, and deviated abnormally to the left in three cases. In another group of 96 patients whose electrocardiograms showed clear evidence of left ventricular hypertrophy, the gradient was not deviated in 64; it was deviated abnormally to the right in 11 and to the left in 11 cases. In two cases there was moderate, doubtfully abnormal, deviation to the right. Moderate, doubtfully abnormal, deviation to the left was seen in eight cases. These findings agree with the results of an earlier cursory examination of the electrocardiogram in hypertension. It can, therefore, be said with confidence that hyperpiesia does not characteristically deviate the gradient to the right. When deviation to the right or left was observed, it was often in association with T-wave changes suggesting myocardial ischemia. Electrocardiograms suggesting infarction were not included. One fact must be stressed, namely, that secondary inversion of

of T_3 . This was the most consistent change observed in this study and is reflected in the deviation of the gradient to the right. Since the ventricular gradient represents the net electrical effect produced by differences in the time course of repolarization, projected onto the frontal plane, and since rightward deviation of \bar{Q} was the most consistent change observed (44 per cent of patients), we feel that abnormality of the gradient is the most reliable electrocardiographic sign seen in acute glomerulonephritis. Furthermore a clockwise rotation of \bar{Q} suggests a delay in repolarization of at least a part of the free wall of the left ventricle similar to that produced by temporary ischemia of the left ventricle of the dog's heart.³⁰⁻³⁴

Various theories have been advanced to explain the changes in the electrocardiogram observed in acute glomerulonephritis. These include injury or spasm of the coronary vessels, edema of the heart muscle due to retention of fluid, accumulation of metabolic end products due to abnormalities in kidney function, and toxemia. Microscopic abnormalities are but rarely seen in the hearts of patients who have succumbed to acute glomerulonephritis.²⁰⁻²⁶ Aside from cardiac dilatation, the necropsy findings give little hint of the factors responsible for the observed abnormalities in the electrocardiogram.

The Cause of the Gradient Changes.—Conflicting reports⁹⁻¹⁵ on the correlation of electrocardiographic findings with the occurrence of hypertension, congestive heart failure, or renal dysfunction have appeared in the literature. We failed to find any significant relationship between electrocardiographic changes and the individual manifestations of heart failure with the exception of the size of the heart. In 92.5 per cent of the patients with clockwise rotation of \bar{Q} , there was evidence of cardiac enlargement while only 48 per cent of those patients with no deviation of \bar{Q} showed an increase in the size of the heart. As we have already said, the probability that these are chance differences is but 1 in about 300,000. Possibly the duration of the cardiac dilatation was a factor in the production of the electrocardiographic abnormalities, but repeated tele-roentgenograms were not made frequently enough for us to check this theory.

There is general agreement that the heart failure in acute glomerulonephritis is accentuated if not caused by the sudden and temporarily continuous elevation of the blood pressure. One of us¹⁶ has demonstrated that a drop in the blood pressure of patients with acute glomerulonephritis usually precedes the disappearance of the symptoms and signs of congestive heart failure unless digitalis has been administered. Langendorf and Pick¹² have suggested that the negative T_1 and slight S- T_1 depression could be explained upon the basis of dilatation of the left ventricle due to the effect of a sudden sustained elevation of the blood pressure on an impaired myocardium. With dilatation of the right ventricle, similar changes might be expected in Leads II and III. Reports of the occurrence of both right and left heart failure in patients with acute glomerular nephritis have been published, but, among our 90 patients, changes in Leads II and III suggesting right ventricular ischemia were seen doubtfully only once. Others have published electrocardiograms presenting apparently unambiguous evidence of myocardial change in the region of distribution of the right coronary artery, always in patients over 30 years of age. We cannot ex-

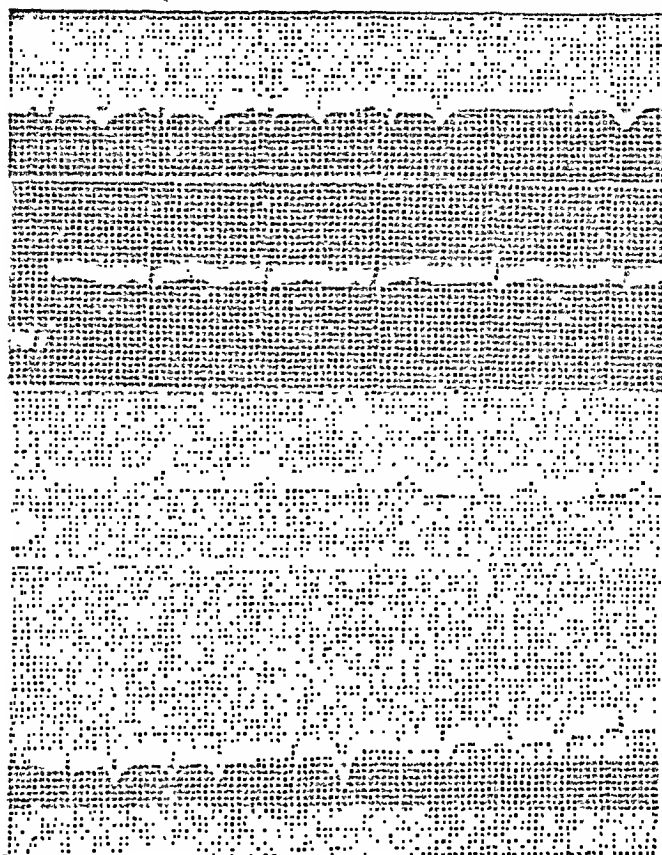


Fig. 1.—Patient L. B., female, aged 7 years. Leads I, II, III, and CF_4 from above, downward. Blood pressure, 180/130. This is a fairly typical electrocardiogram of the patients in our Group 1. There is marked rightward deviation of the gradient. Cycle length changes occur, presumably in association with respiratory movements. Note the relationship between the magnitude of the inverted T wave in Lead I and the cycle lengths. The similar changes in the precordial lead are undoubtedly significant in this case, but occasionally in normal children equal changes in a precordial lead may be associated with respiratory variation in heart position.

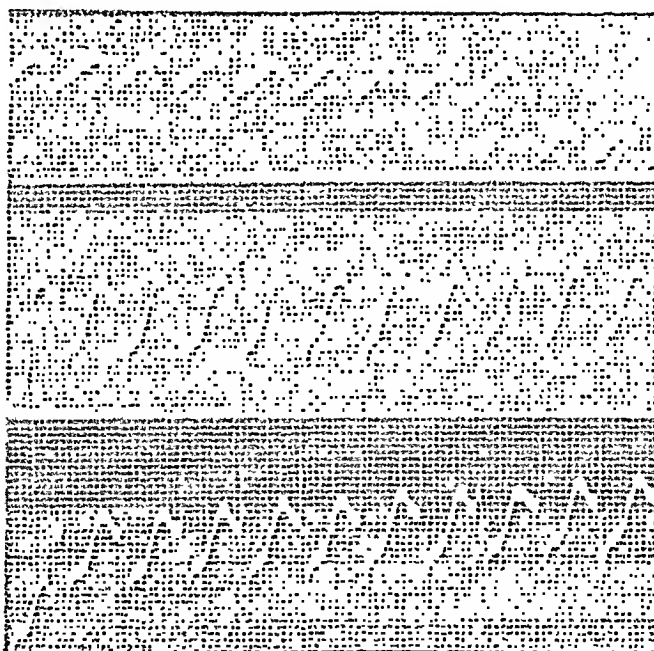


Fig. 2.—Patient G. W., male, aged 2 years. This patient is in Group 3, and did not survive. Leads I, II, III from above, downward. Because of the extreme abnormalities, the gradient was not estimated. The patient was not digitalized. The marked depression of the RS-T segments (which were equally clear in the precordial lead) is interpreted to mean predominant damage of the endocardial left ventricular muscular laminae.

the T wave in Lead I in hypertension does not usually mean deviation of the gradient's direction. In fact, this may occur even when the deviation of \bar{G} is to the left.

The electrocardiograms in a dozen cases of hypertension in toxemia of pregnancy were examined in connection with our present study. In none of these was the gradient deviated. Observation of large numbers of such cases demonstrates that rightward deviation of \bar{G} is uncommon among them. We do not know whether or not cardiac dilatation of the degree seen in glomerulonephritis is commonly observed in the toxemias of pregnancy nor how rapidly the dilatation appears.

In connection with the correlation between cardiac dilatation and gradient changes, the question must be asked: How are these two phenomena related? It may be recalled that in 1927, Visscher and Starling²⁹ found that the oxygen consumption of the ventricular muscle was directly proportional to the diastolic volume. The increased oxygen consumption, of course, is due to an increased metabolic breakdown during systole. In glomerulonephritis the left ventricle, and possibly the right as well, is dilated. This means that the oxygen consumption and metabolic change, are greater than in the normal muscle. The left ventricle, being opposed by a greater peripheral resistance, may be more involved than the right. When the demand for oxygen begins to exceed the supply, fatigue of the muscle ensues as a result of the accumulation of metabolites. The coronary arteries may share in the general arteriolar constriction. By a similar mechanism, myocardial ischemia also induces fatigue and similar electrocardiographic changes.³⁰ Since the subendocardial muscle laminae may obtain oxygen directly or indirectly from the ventricular cavities, they seem to suffer less than the subepicardial laminae. Hence, it is the subepicardial muscle layers of the free wall of the left ventricle which suffer most. The precordial leads, however, suggest that not all parts of the free wall are equally affected, but we do not have the data necessary to enable us to localize definitely the most commonly affected regions.

According to this interpretation, the slow repolarization both in myocardial ischemia and in glomerulonephritis is associated in some way with the chemical changes of local myocardial fatigue. In both conditions, the Q-T interval is prolonged.

Other Parallels Between the Electrocardiographic Changes in Ischemia and in Acute Glomerulonephritis.—It has just been noted that the Q-T interval is prolonged on the average in Group 1. Another resemblance between myocardial ischemia and acute glomerulonephritis is in the form of the T waves, which are the same in both conditions, although the very large, abnormal, T waves sometimes found in ischemia are not often seen in nephritis.

In myocardial ischemia, when abrupt changes in cardiac cycle length occur, as in premature beats, the T wave is usually more abnormal in appearance after the longer pauses.^{19, 35} This same type of change was observed in several of our cases in association with the cycle-length changes of sinus arrhythmia and is illustrated in Fig. 1.

axis of the ventricles, called $S\bar{H}$, a small net area of QRS in the normal heart implies rotation such that the base is farther forward, or the apex farther backward than usual. A large A_{QRS} implies the reverse. Clockwise or counterclockwise rotation of the ventricles about $S\bar{H}$ as an axis, the apex being viewed, may change the magnitude, A_{QRS} , and causes great changes in the form of the QRS complex.^{41, 42}

The spatial T-wave axis points from those parts of the muscle which become repolarized latest to those which are repolarized earliest. Clearly, however, the relative timing of completion of repolarization in any fiber membrane will depend not only upon the rate of its repolarization but also upon the timing of its depolarization. A change in the form or width of the QRS complex, as in hypertrophy of a ventricle or in bundle branch block, will change the relative times at which fiber depolarization occurs and will necessarily influence the relative timing of each stage in repolarization. Hence, *invariably*, if the muscle is normal and no great change in cycle length or heart movement in systole occurs, a change in the magnitude of A_{QRS} is associated with an equal and opposite change in the magnitude of the T wave. Not only is the T wave affected by such QRS changes which may occur in one individual, but it is also modified by the individual differences in the QRS complexes of different persons. For every normal form of the QRS complex and the magnitude, A_{QRS} , there is a different normal range in form, direction, and magnitude of the T wave. In some normal, though unusually placed hearts, an inverted T wave is normal in Lead I, and a typically large, normal appearing T wave is quite abnormal. In other, less unusual cases, an upright T wave in Lead III must be regarded as abnormal. Once the effect on the electrocardiogram of positional variation is understood on a theoretical basis, these facts are quite easy to grasp. Empirical observation on the other hand may, indeed, teach the normal ranges, but only after many years of experience and close attention to the subject.

As we have seen, the T wave, which is due to repolarization, is affected by heart position and by the normal variations in A_{QRS} . It should be clear, therefore, that for the study of many problems it is desirable to have a method of measuring the electrical effect of the differences in time course of repolarization of the different muscle elements. This is the effect, which, in general, produces the usual upright T waves of Leads I and II. The method has been provided by Wilson and his co-workers; and the net electrical effect of the difference in time course of different elements, as this is projected onto the frontal plane, he has called the ventricular gradient.³⁷ As he and also Bayley³⁰⁻³⁴ have pointed out, the net area of the total ventricular complex, QRS-T, in any limb lead is equal to the projection of the gradient, G , onto the line of that lead. Like other axes, G is the projection onto the frontal plane of a spatial axis, SG . Unlike A_{QRS} , the magnitude of the gradient, G , is affected by a number of physiologic changes, and especially by heart rate. The spatial direction of SG , of course, also affects the magnitude of the projected gradient, G .

The axis of the T wave has a wide range of variation in direction in different normal hearts and in the same heart at different heart rates. G has a smaller directional range. The average direction is about $+40$ to $+45^\circ$,⁴³ with the extremes ranging from about -15 or -20° to $+90^\circ$. However, when the direction of the gradient is compared with its average direction for each intrathoracic heart position of rotation about longitudinal, transverse, and antero-posterior axes, its actual direction, in the slowly beating hearts of recumbent (and most seated) persons ranges only from 23° to the left to 15° to the right of this estimated direction. If the heart rate is greater than 50 or 60 beats per minute, the range to the left, but not to the right, must be extended 4.5° for every increment in rate of 30 beats per minute.⁴³ The range here given is placed at three standard deviations from the mean found in a series of 242 normal persons, including 78 children and 24 persons over 50 years old. Hence only one normal person in about 400 should have a gradient outside this range, with the following exception. If A_{QRS} is of average magnitude, that is, about 5.5 or 6 units, or above, the range can be narrowed 3° on the right.⁴³ If A_{QRS} is very small (2 units or less) the range should be widened by 4° or 5° at either end. These statements hold when the anatomic axis of the heart, \bar{H} (the "projection" of $S\bar{H}$ onto the frontal plane or A-P x-ray film) is estimated from the QRS complex of the electrocardiogram itself. When \bar{H} is measured on the roentgenogram, the range is not appreciably narrowed.⁴³ These state-

In myocardial ischemia, as the degree of oxygen lack increases, the intensity of polarization of certain cell membranes decreases, and the ischemic condition has then passed over into the stage Bayley has defined as injury.³⁶ In a few of our cases, the injury, by this definition, had apparently begun. Fig. 2 is an illustration of a severe case. The patient did not survive.

In no significant respect did the T-wave changes found in Group 1 differ from the changes observed in myocardial ischemia.

The Precordial T Wave in Glomerulonephritis.—In normal children, at least those below the age of 10 or 11 years, the T wave is usually inverted in Lead CF_2 and upright in Lead CF_3 . There was no exception to this finding among 12 cases chosen for this purpose. In children the T wave in CF_4 is usually upright, but sometimes it is inverted. In 24 cases among those of Group 1, the T wave, even though recorded from a point on the thorax over the left ventricle, as judged from the form of the QRS complex (corrected for the left leg potential), was inverted, low, or diphasic. In certain other cases, however, although the T wave was inverted in Lead I, it was upright at CF_4 after correction for the foot potential. This is one indication of the truth of a statement made elsewhere in this paper, namely, that the whole free left ventricular wall is not equally affected in the nephritic patients of Group 1.

It was expected that, unlike the normal, the T wave at CF_2 or CF_3 would often or usually be upright when the T was inverted in Lead I. Unfortunately, in only two such cases was the electrode placed definitely over the right ventricle. In one of these, the T was upright; in the other case it was inverted.

APPENDIX

The Electrocardiogram: Theoretical Considerations.—As in other branches of medical diagnosis, as electrocardiography has become less empirical and more quantitative, it has been found possible to define more precisely the boundary between the normal and the abnormal. With respect to the ventricular complex, QRS-T, the electrical effects of two processes are determined. These are depolarization of the muscle, which leads to production of the QRS complex, and repolarization, which produces the T wave. As projected onto the frontal plane of the body, these processes produce complexes of a wide variety of normal form and magnitude, for much the same reason that a person's shadow at mid-day differs greatly from that just before sunset. The electrical axes, found from the limb leads, whether mean or instantaneous, are the projections onto the frontal plane of spatial axes. The projected magnitudes may be large or small depending upon whether the spatial axes nearly parallel the frontal plane or are nearly perpendicular to it. In their directions in relation to the mass of ventricular muscle these axes are relatively constant in different hearts. However, since the hearts of different persons exhibit a wide range of position within the thorax, so do the projected directions and magnitudes of the axes show a great range.

The mean manifest QRS axis, hereinafter called \hat{A}_{QRS} , is defined in direction in terms of the angle alpha of Einthoven, and in magnitude in microvolt-seconds. The area of a small rectangle formed by the time and millimeter lines, with the usual timing and standardization, is 4 microvolt-seconds. From the net area of the QRS complex, above (+) or below (-) the base line of the electrocardiogram in any two limb leads, the direction and manifest magnitude (to be called A_{QRS}) of the mean manifest QRS complex can be found by methods previously outlined.³⁷⁻³⁹ Rotation of the ventricles about a transverse axis will cause great variations in this net magnitude, A_{QRS} , which may normally range from -2 to +13 units of 4 microvolt-seconds each.⁴⁰ When the heart is not rotated about the longitudinal anatomic

ments may not apply to children under 5 or 6 years old, although 19 normal children between the ages of 2 and 5 years, inclusive, came within the range as given.

It should be emphasized that, in the study of certain types of electrocardiographic problems, the semiquantitative approach herein described is essential. We have found a number of electrocardiograms which, empirically, would be called either normal or doubtful, but which are clearly abnormal when subjected to brief analysis. On the other hand, we have in the past called certain electrocardiograms abnormal which, on re-examination by the gradient method, have proved to be within normal limits. The electrocardiogram of Fig. 3 was interpreted as within normal limits. Yet the gradient is deviated by 13 degrees from its estimated normal direction. Fig. 4 shows another example. This case was recent, and the gradient deviation was recognized. After the blood pressure had fallen, the normal electrocardiogram of Fig. 5 was taken from the same patient.

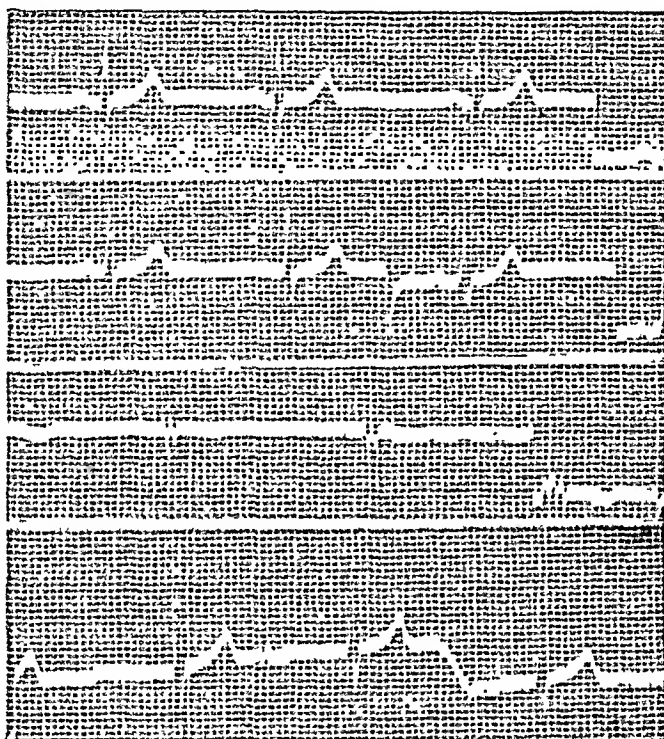


Fig. 5.—Same patient as in Fig. 4. The blood pressure had fallen to 125/70. Leads as before. A_{QRS} is $+20^\circ$; A_{QRS} is 3.5 units. G is $+22^\circ$ (versus 57° in Fig. 4); G is 11.9 units. The increase in G since the earlier electrocardiogram is mainly in association with the increase in A_{QRS} , a usual finding. H was estimated at $+32^\circ$. The estimated normal position of G was $+28^\circ$. The 6° diversion of G to the left of its estimated position is quite normal. The U waves are less prominent than in Fig. 4. (Artifacts appear in Leads II and CF₄.)

Method of Estimating the Direction of the Anatomic Axis, H .—The best method is to sketch the general form of the QRS loop of the vectorcardiogram from inspection of the limb lead QRS complexes,⁴⁴⁻⁴⁶ and use a model of the spatial loop, which also has indicated upon it the axes, $S\hat{A}_{QRS}$, SG , and $S\hat{H}$ (Fig. 6). As a poor substitute for this method, the diagrams of Figs. 7, 8, and 9 are presented. These are not absolutely accurate, and an error of 5 or 10° in estimating H may sometimes be involved in using them; but since an error of this magnitude in the estimated H introduces only half the error into the estimated G , they can be used, with extension of the range of normal by about 2° in either direction. Explanations of Figs. 7, 8, and 9 are given in the legend.

The axes, \hat{A}_{QRS} and G , are obtained by measuring the electrocardiogram, as previously explained.^{38, 39} Having found these axes, refer to Table II. For example, \hat{A}_{QRS} may be $+70^\circ$, and its magnitude may be 5 units. G may be $+55^\circ$. H has been estimated, by the method of Fig. 6, as $+40^\circ$. The angle between \hat{H} and \hat{A}_{QRS} is, therefore, 30° . This figure is found in the column on the left (Table II). Above, in the horizontal column, find 5 units. Where the lines intersect is the figure, 14. This is the number of degrees to add to H to find the

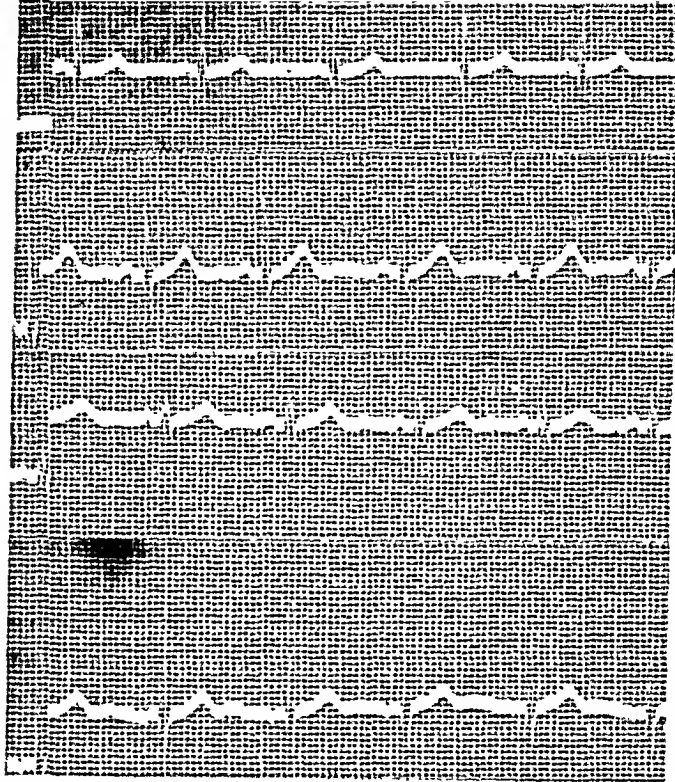


Fig. 3.—Patient J. L., male, aged 14 years. Blood pressure, 170/100. Leads I, II, III, and CF_4 from above, downward. When this electrocardiogram was taken in 1941, it was interpreted as within normal limits. $AQRS$ is measured at $+39^\circ$; $AQRS$ is about 3.4 units (13.6 microvolt-seconds); G is $+59^\circ$; G is about 13.5 units. It is estimated at $+49^\circ$, and G is estimated at $+46^\circ$. Thus the gradient as measured lies 13° to the right of its usual normal position. At this age, and when the measurements are reasonably reliable as in this case, this deviation (or diversion as Bayley calls it) of G may be regarded as definitely abnormal. The U waves are, perhaps, slightly prominent in the precordial lead. No later electrocardiogram was taken in this case.

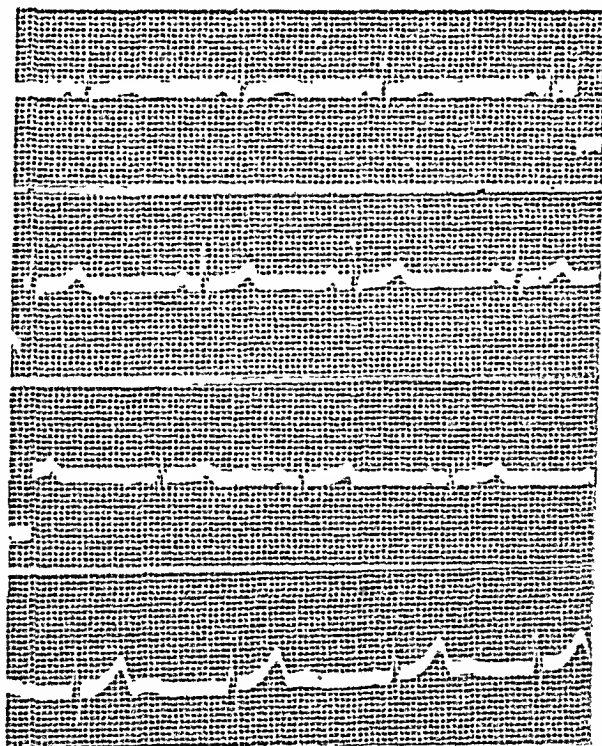
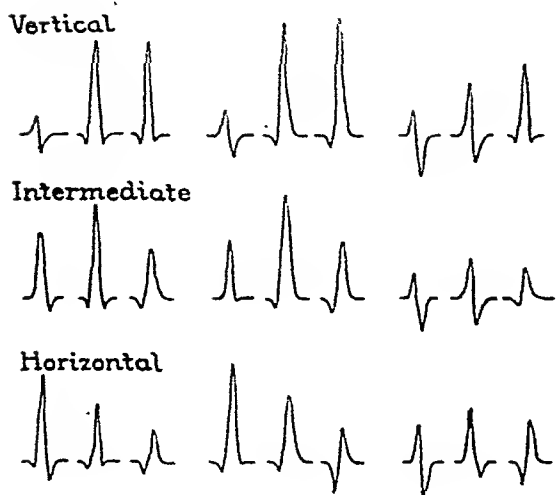


Fig. 4.—Patient A. L., male, aged 16 years. Blood pressure had ranged from 150/100 to 230/140 before this electrocardiogram was taken. Leads I, II, III, and CF_4 from above, downward. $AQRS$ is $+33^\circ$; $AQRS$ is 2.2 units. G is $+57^\circ$; G is 7.9 units. Estimated $\bar{\alpha}$ is $+33^\circ$, and the estimated normal position of G is $+33^\circ$. Hence, G is deviated 24° to the right. This electrocardiogram was recognized as an example of abnormal gradient deviation in 1943. Two years earlier we may have noted the relatively low T wave in Lead I, but would have had no criterion for judging whether or not it was a normal variant. The electrocardiogram is normal in other respects. The U wave in the chest lead is somewhat prominent, suggesting left ventricular overactivity.

MODERATE CLOCKWISE ROTATION



STRONG CLOCKWISE ROTATION

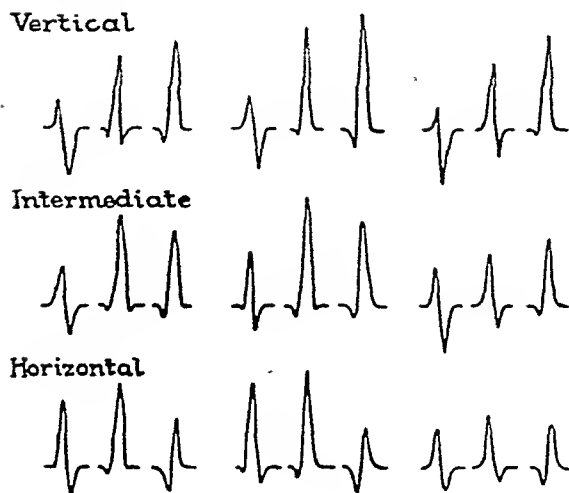


Fig. 7.

NO ROTATION

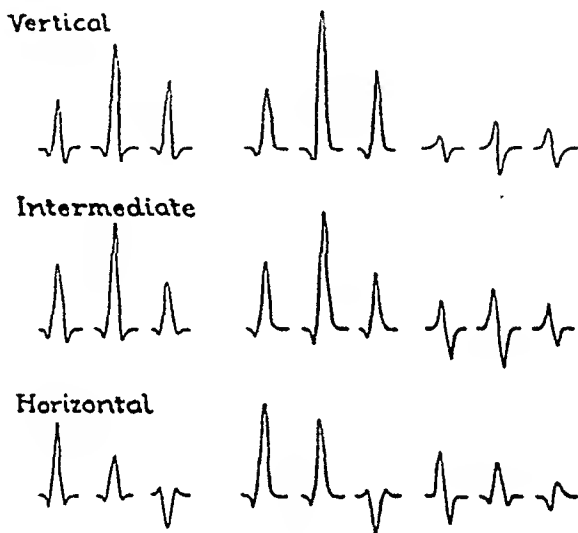
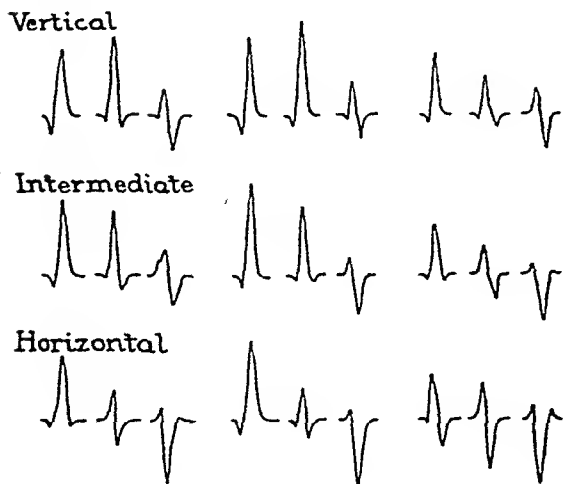


Fig. 8.

STRONG COUNTERCLOCKWISE ROTATION



MODERATE COUNTERCLOCKWISE ROTATION

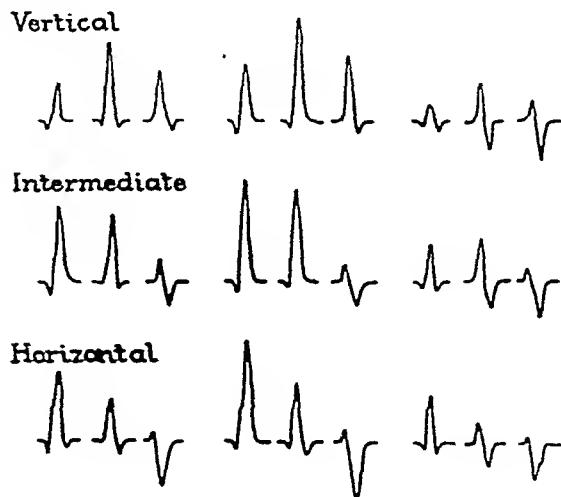


Fig. 9.

Figs. 7, 8, and 9.—(For legend see opposite page.)

estimated position of G . This position in this case is $+54^\circ$. The position, from measurement of the electrocardiogram was $+55^\circ$. The actual G is 1° only to the right of the estimated G , much less than the errors involved in the measurements. In this example, \hat{A}_{QRS} lay to the right of \hat{H} . If there is appreciable counterclockwise rotation about $S\hat{H}$, \hat{H} may be $+40^\circ$ as before, but \hat{A}_{QRS} may be at -2° . The angle between these axes is 42° . If \hat{A}_{QRS} in this case is

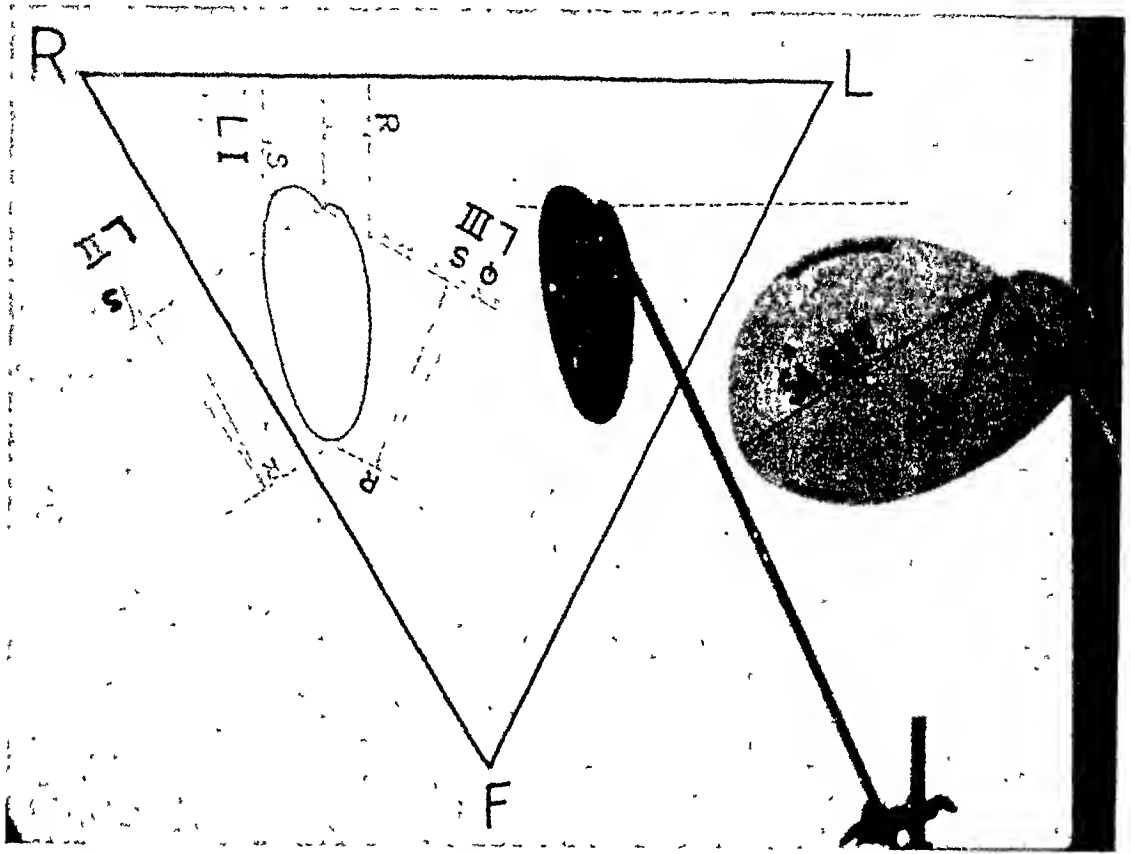


Fig. 6.—The loop on the reader's left within the triangle is the QRS loop derived from the QRS complexes, as shown. On the right, outside the triangle, is the spatial QRS loop, with the mean spatial axes. $S\hat{A}_{QRS}$ and $S\hat{C}$ marked thereon, together with the spatial longitudinal anatomic axes, $S\hat{H}$. These axes are shown as if originating from a common origin at the notch in the loop. The arrows indicate the direction of rotation of the instantaneous axes. The form of the loop is shown fairly well, the length of $S\hat{A}_{QRS}$ from the origin to its point being slightly greater than double the maximum width of the loop. The spatial loop is placed so that the form of its shadow (size depending on size of model) most nearly resembles the general form of the QRS loop derived from the limb leads. For the large majority of electrocardiograms with normal QRS complexes, the angle between the dashed line and the shadow of $S\hat{H}$ (here about 65°) will be found to correspond closely to the longitudinal anatomic axis of the ventricles, as found from the roentgenogram taken in the same body position as the electrocardiogram. This method may tend to estimate very vertical H axes as several degrees more vertical than the true axes, whereas very horizontal axes often appear somewhat more horizontal than they actually are. The loop is a compromise which best fits all cases. When disease or hypertrophy changes the QRS complex, the method is no longer applicable, although it is fairly accurate in moderate left ventricular hypertrophy. Properly applied, estimates of H by this method should be correct within $\pm 7^\circ$ in about 90 per cent of normal persons over 5 years of age.

Figs. 7, 8 and 9.—In each of the figures, 7, 8, and 9, the heading in capital letters refers to rotation of the heart about the longitudinal anatomic axis, $S\hat{H}$. The direction of rotation is that which would be seen if the observer viewed the apex of the ventricles. The words, vertical, intermediate, and horizontal, refer to rotation about an anteroposterior axis, according to established usage. On each horizontal line, three groups of QRS complexes are shown. In each group the first is Lead I, the second is Lead II, and the third is Lead III. In the first vertical row of QRS complex groups, the apex (or $S\hat{H}$) has an average forward projection; in the second vertical row, $S\hat{H}$ points farther forward than usual; in the third vertical row, $S\hat{H}$ has little or no forward direction and nearly parallels the frontal plane. In general, H for the vertical groups is at about $+55^\circ$; for the intermediate group, H is at about $+40^\circ$; for the horizontal group, H is about $+20$ to $+25^\circ$ in Figs. 7 and 8, and about $+25^\circ$ in Fig. 9. The QRS complexes in Fig. 6 are roughly intermediate between those of the top groups in the fourth and fifth vertical columns of Fig. 7. Although Fig. 6 indicates that H is about $+65^\circ$, 60° would be more nearly correct.

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4.5 units, the number of degrees found in Table II is between 16 and 18, or 17°. Since, in distinct rotations, \bar{A} is between \bar{A} and \bar{A}_{QRS} , the 17° is subtracted from the \bar{A} of 40°, giving +23° as the estimated position of \bar{G} . In a case of this sort, if the heart rate is high, the T wave in Lead I may be low or even inverted, and much higher in Lead III. When \bar{A} is +40°, however, such strong counterclockwise rotation is uncommon.

If there is serious doubt about the position of \bar{A} , it is better not to rely on the method. Yet in our control series of 242 cases, not a single electrocardiogram was rejected because of doubt concerning \bar{A} . In one test of the 164 adults in that series, \bar{A} was arbitrarily called +40° (near the average) and \bar{G} was then estimated. This significantly increased the range, proving that the estimate cannot be dispensed with.

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3. There is an absence of the specific pattern in the electrocardiogram in animals with pulmonary embolism after bilateral cervical vagotomy^{1, 2, 5} as compared with its occurrence when the vagi are intact.

4. Effects similar to those described in 1, 2, and 3 occur after atropinization as compared to pulmonary embolism before its use.^{3, 5}

5. There is a beneficial clinical effect of atropine on the course of pulmonary embolism.³

Critique of Evidence.—

When this evidence is surveyed critically, adequate alternatives can be offered for the findings.

Thus.—

1. The phenomena mentioned in 1 and 2 of A may indicate a reflex mechanism, but this may be in the nature of pulmonopulmonary reflex,⁷ raising pulmonary resistance beyond that caused by the actual embolic closure. A reflex bronchiolar constriction may also occur increasing the effort of breathing. The latter might possibly be lessened by vagus section and by atropine. The existence of such reflex mechanisms would increase the work of the right heart which could make for a relative coronary insufficiency on a purely dynamic basis.⁷ A reflex origin of the ectopic rhythms may be involved, and this might be propagated over the vagi, contributing to the dynamic handicap and to the chance of irreversible ventricular fibrillation. If any or all of these reflexes do occur in pulmonary embolism they may operate over pathways other than the vagus nerve trunks.

2. Statement 3 of A does not exclude a purely dynamic coronary insufficiency due to right heart congestion, increased work of the right heart, and decreased aortic pressure, all resulting from the pulmonary arterial obstruction. The factors involved which lead to such a dynamic relative coronary insufficiency have been described in detail by us.^{7, 10, 13} They could explain the coronary-like electrocardiogram without invoking a reflex coronary constriction.

3. Statement 4 of A is not universally accepted. The evidence is contradictory.⁸ Our own results in the dog have suggested that the vagi are actually cholinergic coronary vasodilators⁹; the contrary evidence is far from convincing to us.

4. The statements in B may be purely chance variations. Survival rates of animals and the frequency of ectopic rhythms and electrocardiographic changes must be based on larger series than those reported in order to be statistically significant. Our own experience^{7, 10} and that of others¹² have shown the great variability of the results of pulmonary embolism when the vagi are intact. Evidence comparing vagotomized with nonvagotomized animals therefore cannot be considered direct evidence unless statistical analysis shows the differences to be significant and this has not yet been demonstrated. This is particularly true of the frequency of the occurrence of the specific electrocardiographic changes with which the present report is concerned.

IS THERE A VAGAL PULMONOCORONARY REFLEX IN PULMONARY EMBOLISM?

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THE view has been held¹⁻³ that the dynamic disturbances occurring in cases of pulmonary embolism are to a large extent attributable to a reflex arising in the lungs which produces vasoconstriction of the coronary vessels via efferent vagal fibers. This has been called the pulmonocoronary reflex. The evidence presented to support this view is in part indirect and in part direct. It may be summarized as follows:

A. Indirect Evidence.—

1. The clinical and experimental effects of pulmonary embolism are often out of proportion to the apparent degree of occlusion of the pulmonary vascular circuit. Thus it is believed that some reflex mechanism must be operative.

2. There is a rich afferent nerve supply to the lung vasculature over which reflexes are known to be established which affect the respiratory and circulatory apparatus, including ectopic rhythms of the heart.

3. An electrocardiographic pattern simulating that seen after coronary occlusion occurs in pulmonary embolism both clinically and experimentally. Therefore, it is argued, the electrocardiogram presents evidence of coronary insufficiency.^{2, 3} It is maintained that this coronary insufficiency is due to a reflex coronary vasoconstriction.

4. Since it has been claimed on the basis of experimental observations⁴ that the vagi are coronary constrictors, it is further argued that the reflex vasoconstriction in pulmonary embolism is a pulmonocoronary reflex having its afferent path in the nerve fibers coming from the lung blood vessels and its efferent path in the vagus fibers going to the coronary vessels.

B. Supposed Direct Evidence.—

1. There is a higher survival rate of animals in which pulmonary embolism is induced after bilateral cervical vagotomy^{1, 2, 5} when compared with those in which the vagi are intact.

2. There is a less frequent occurrence of ectopic rhythms in animals in which pulmonary embolism is induced after bilateral cervical vagotomy^{1, 2, 6} when compared with those in which the vagi are intact.

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B. Pulmonary Embolism.—Five of eight animals in this series showed definite changes in the electrocardiogram following pulmonary embolism. The results are exemplified by Figs. 3, 4, and 5. Pulmonary embolism was found to invert the T wave in Leads II and III in most instances (Fig. 3), but in others S-T depression in these leads was the main change (Fig. 5). In some, the

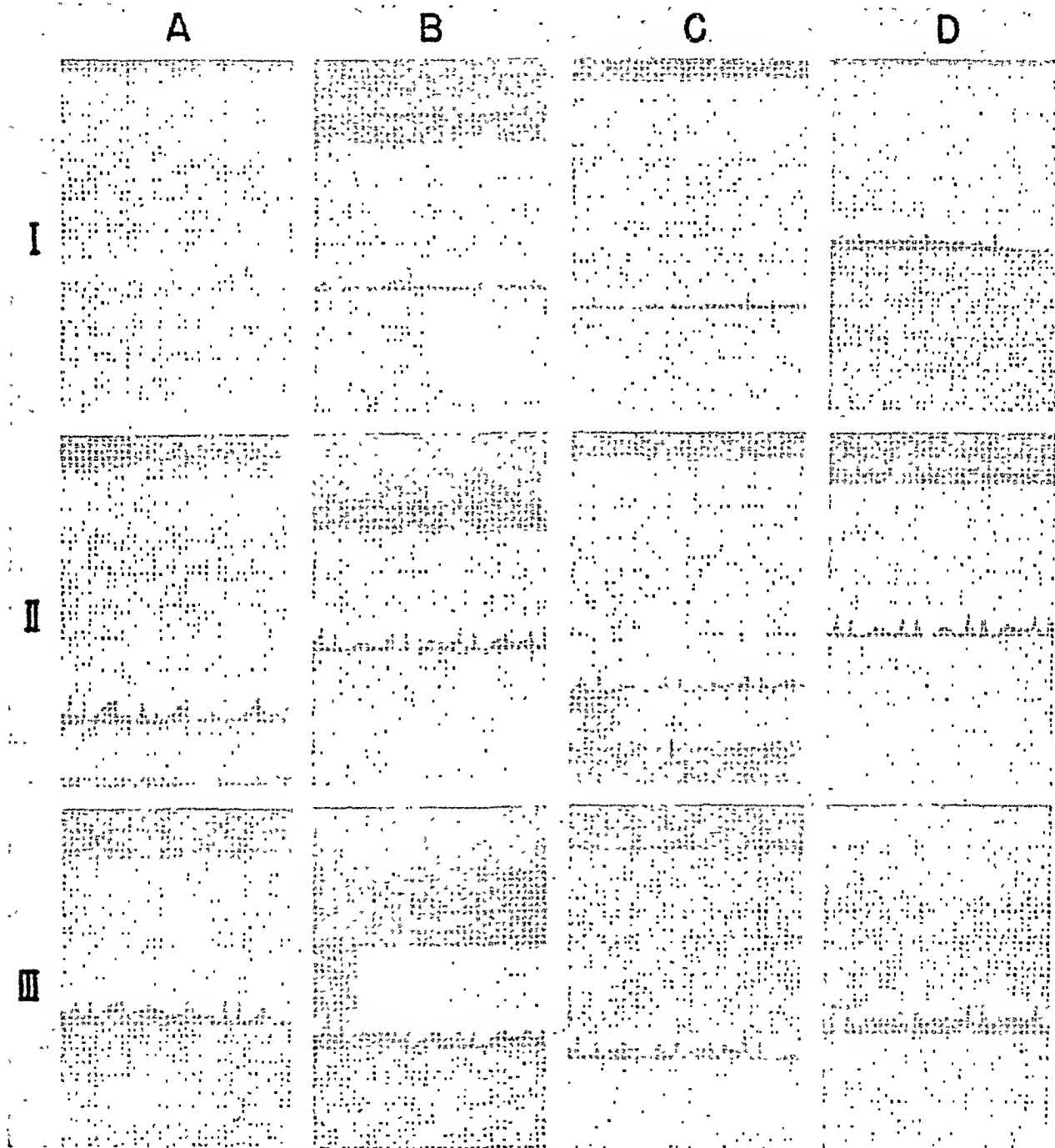


Fig. 1.—Control experiment. *A*, After anesthesia, 25 mg. of nembutal per kilogram. *B*, Eight hours later; the dog had received a total of 38 mg. of nembutal per kilogram and 100 c.c. of isotonic saline in the interim. *C*, Five minutes later, immediately after bilateral cervical vagotomy. *D*, One hour after *C*.

T-wave inversion changed to an S-T depression hours later (Fig. 4). In none of these animals did subsequent bilateral vagotomy alter the postembolic electrocardiogram.

In short, the evidence presented for the presence of the pulmonocoronary reflex over the vagi is unconvincing, and other equally valid explanations for the findings, supposedly supporting this view, can be advanced.

It was therefore deemed advisable to reinvestigate this question directly in a simple way, namely, to see if sectioning of the vagi in a dog would abolish the specific electrocardiographic contour produced by pulmonary embolism and cause the electrocardiogram to revert toward normal. The present report deals with the results of such an investigation.

METHODS

Dogs weighing between 11 and 13 kg. were used in this study. They were anesthetized with nembutal (25 mg. per kilogram), and supplementary nembutal was given in the course of the experiment when necessary to keep the dogs at a surgical level of anesthesia. Massive emboli to the lungs were produced in the manner previously described.¹⁰ However, the size of the emboli was smaller (0.5 to 1 c.c. capacity, as against 5 c.c. in the previous studies) because smaller-sized dogs were used, and because multiple successive emboli (anywhere from one to 16) were employed. Each embolus was forced in with 100 c.c. of saline. In order to avoid electrocardiographic changes which might result from changes in the position of the animal,¹¹ a special trough animal board was constructed which minimized the change in the animal's position. The emboli were labeled so that their location and effect on the electrocardiogram could be correlated. Passage of the emboli in most cases was made under fluoroscopic control. Autopsy was performed to verify the location of the emboli.

A control record was taken and only those animals which showed positive or diphasic T waves in Leads II and III were used for embolization. After an embolus reached the pulmonary vessels, as evidenced by fluoroscopy, records were taken every thirty minutes until definite changes from the control appeared and persisted. When necessary, to produce a definite change, more emboli were passed. After definite persistent changes were obtained, both vagi were cut in the neck and a record was obtained immediately and every fifteen minutes thereafter for an hour. In some animals further emboli were then passed.

As a control, the procedures of anesthesia, cannulation of the jugular vein, periodic saline infusion, and vagotomy were performed in several animals, but no emboli were passed. Electrocardiograms were taken every hour before vagotomy and every twenty minutes after vagotomy.

RESULTS

A. Controls.—Four normal control animals were used in this study. The results in the controls are shown by Figs. 1 and 2. Slight changes in the S-T deviation and of the size of the T waves occurred, but the changes were not significant. In three of the four dogs, vagotomy had no effect. In one animal (Fig. 2) a transient change in the electrocardiogram appeared immediately after vagotomy. These controls serve to show that in any changes following embolism the emboli themselves must be the causative factors.

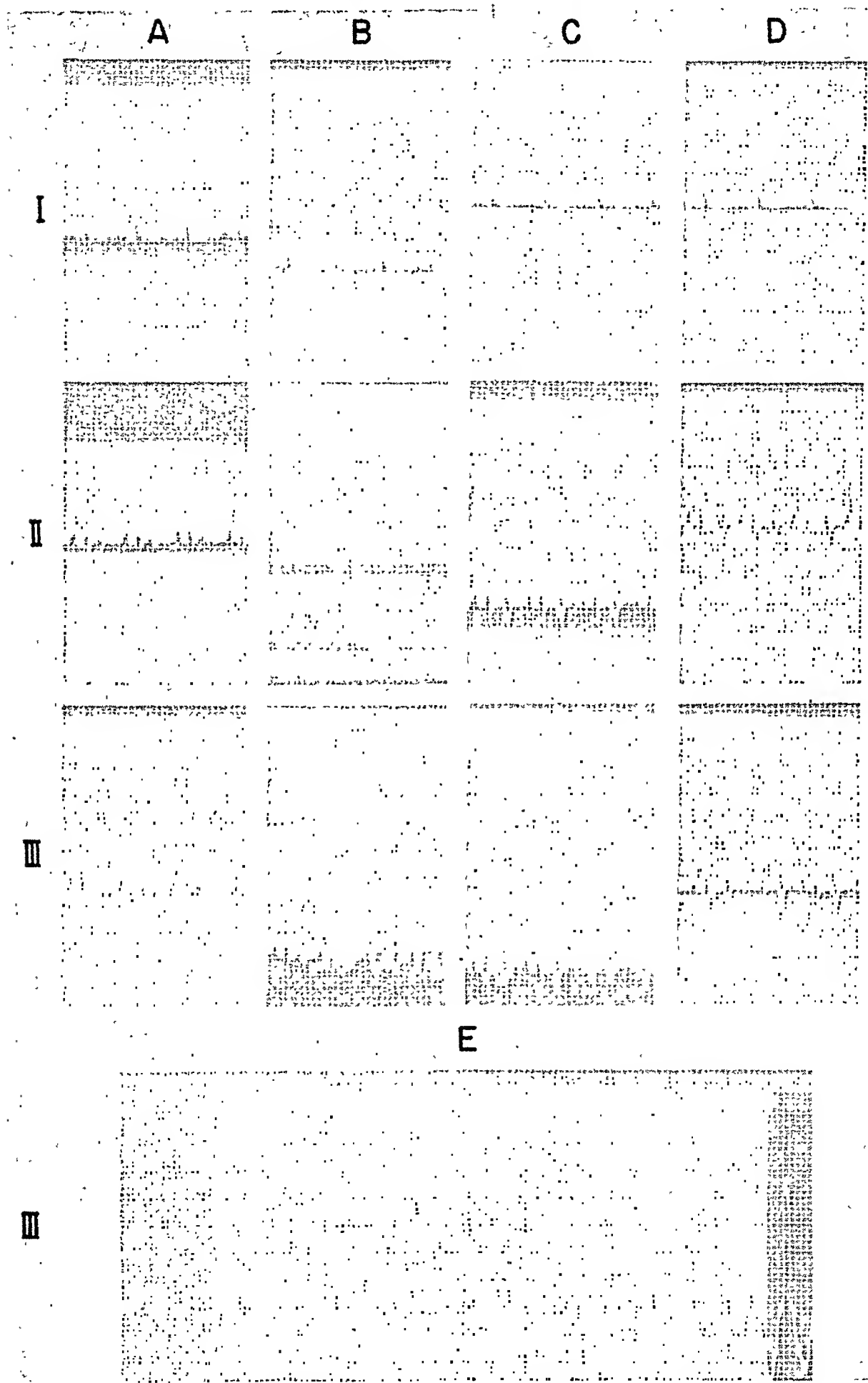


Fig. 3.—(For legend see opposite page.)

Furthermore, in the course of the preliminary experiments, pulmonary embolism was produced in seven dogs after bilateral vagotomy, and in five, electrocardiographic abnormalities appeared similar to those described.

Cardiac irregularities were commonly seen during the passage of the emboli.⁷⁻¹⁰ These consisted usually of frequent ventricular premature systoles

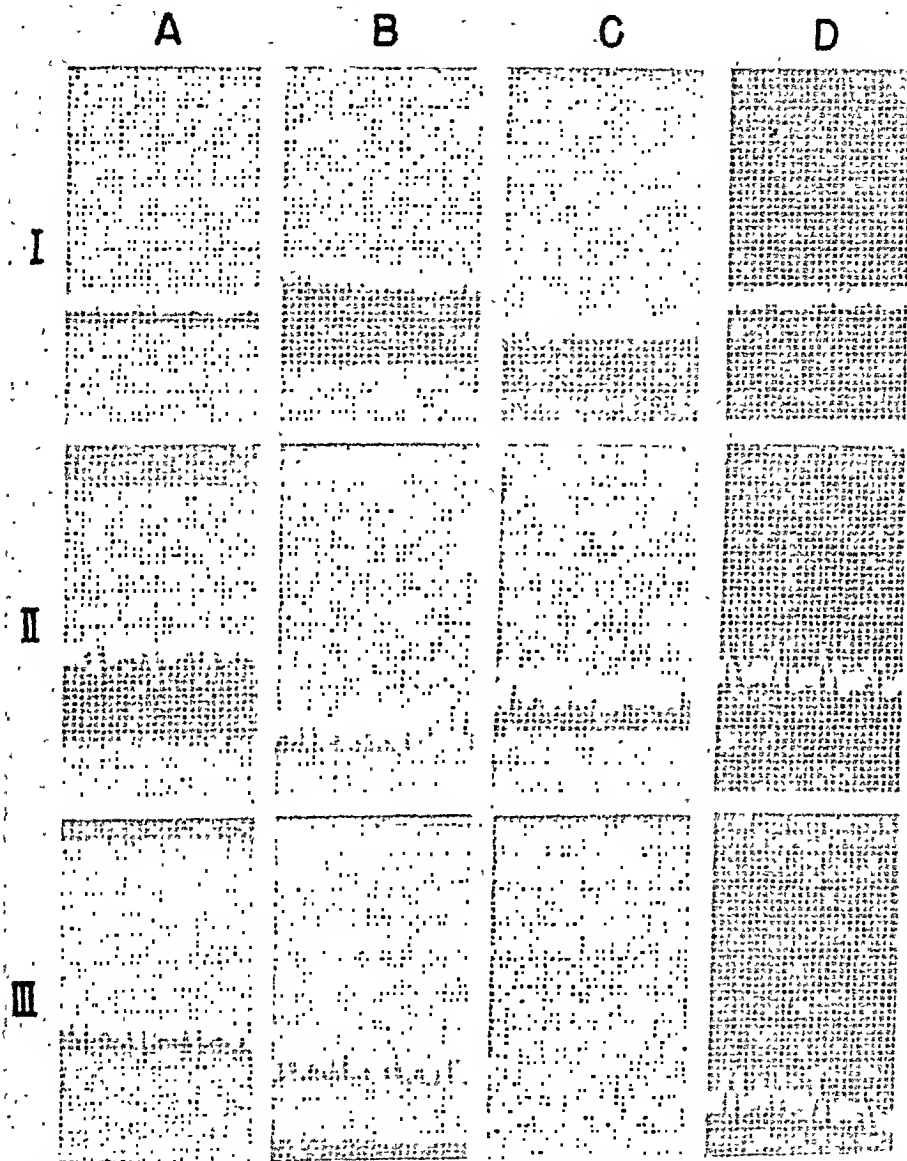


Fig. 2.—Control experiment. *A*, After anesthesia, 25 mg. of nembutal per kilogram. *B*, Six hours later; the dog had received a total of 38 mg. of nembutal per kilogram and 200 c.c. of isotonic saline in the interim. *C*, Two minutes later, immediately after bilateral cervical vagotomy. *D*, One hour after *C*.

Fig. 3.—Pulmonary embolism experiment. *A*, Control after anesthesia, 25 mg. of nembutal per kilogram. *B*, Five hours later; the dog had received a total of 7 mg. of nembutal per kilogram and 450 c.c. of isotonic saline in the interim, as well as three pulmonary emboli, two in the right and one in the left main pulmonary arteries. *C*, Five minutes later, after bilateral cervical vagotomy. *D*, One hour after *C*. *E*, Two hours after *D*, the dog had received 6 more emboli, 4 in the common, 1 in the right main pulmonary artery, and another (the last) in the cavity of the right ventricle in the interim. This record shows a paroxysmal ventricular tachycardia. The dog died of ventricular fibrillation fifteen minutes after the last embolus.

changes can be produced in bilateral vagotomized animals. (3) Sectioning the vagi in the neck does not cause the electrocardiographic abnormalities to disappear. This confirms the observation on one animal made by Love and his co-workers.¹² (4) There is a wide range in the degree to which pulmonary

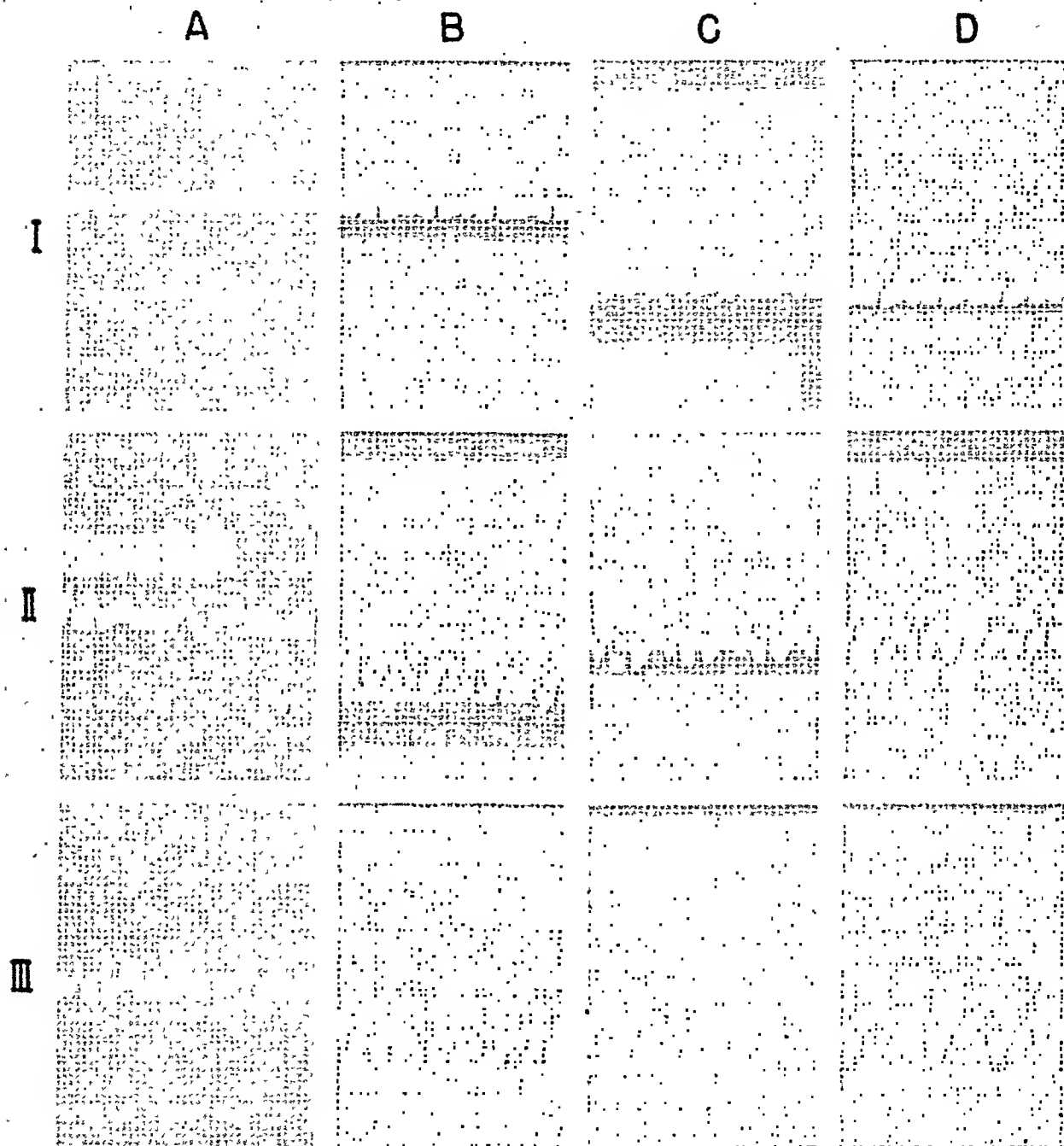


Fig. 5.—Pulmonary embolism experiment. *A*, Control after anesthesia, 25 mg. of nembutal per kilogram. *B*, Thirteen hours after *A*; the dog had received a total of 29 mg. more of nembutal per kilogram and 1,400 c.c. of saline in the interim as well as ten pulmonary emboli located in the common and right and left main pulmonary arteries. *C*, Ten minutes after *B*, immediately after bilateral cervical vagotomy. *D*, One hour after *C*.

emboli produce the electrocardiographic abnormalities, and the number of emboli needed to produce electrocardiographic changes are variable. (5) The time of appearance of the electrocardiographic changes after embolism is also variable depending apparently on the accretion of thrombi upon the embolus.

and paroxysmal ventricular tachycardia. They occurred also in vagotomized animals. Two animals died of ventricular fibrillation: one, two minutes after passage of the fifteenth embolus, the other, fifteen minutes after the passage of the ninth. Both of these animals had been vagotomized and in both the fatal embolus was found lodged in the right ventricular cavity.

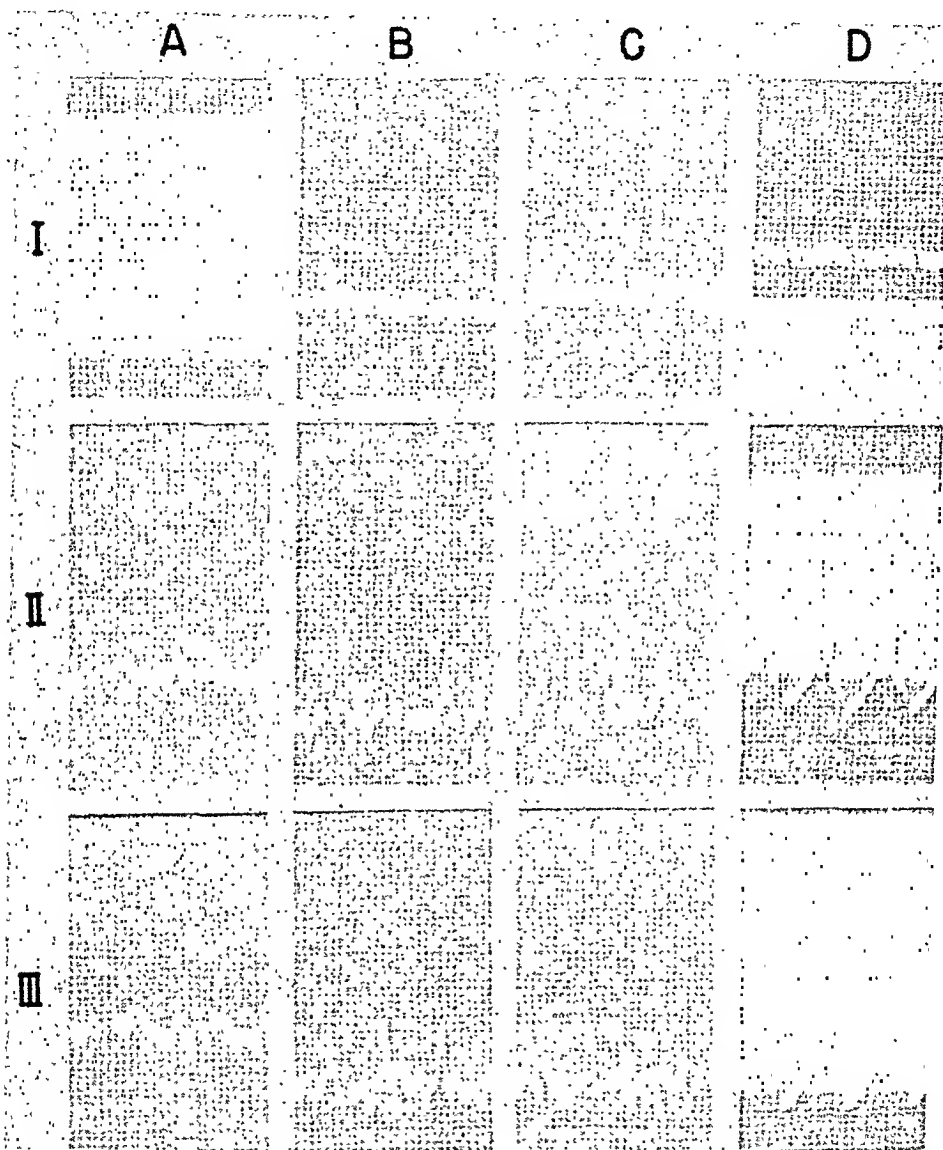


Fig. 4.—Pulmonary embolism experiment. *A*, Control after anesthesia, 25 mg. of nembutal per kilogram. *B*, Forty minutes later; the dog had received one embolus in the main right pulmonary artery. *C*, Ten minutes later, shortly after bilateral cervical vagotomy. *D*, Twenty hours after *C*, the dog had received a total of 54 mg. of nembutal per kilogram in the interim and showed very slow, deep breathing at this time.

The emboli in the pulmonary vasculature were found in the common pulmonary artery in half the cases and in the other half they were equally divided between the major right and major left branch.

DISCUSSION

Our results clearly indicate that: (1) Experimental pulmonary embolism often produces definite electrocardiographic changes, thus confirming our previous results^{7, 10} and those of others.^{1-3, 5, 12} (2) Similar electrocardiographic

UNSTABLE T WAVES IN LEADS II AND III IN PERSONS WITH NEUROCIRCULATORY ASTHENIA

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INTRODUCTION

ALTHOUGH much has been written concerning the psychiatric and clinical aspects of neurocirculatory asthenia, there is only a meager number of contributions which refer to the electrocardiographic features of this disorder. Of these reports, most are concerned with distortions of the T wave in Leads II and III¹⁻⁴ but, with a single exception,⁴ the emphasis has been placed upon the appearance of such changes only when the electrocardiogram is obtained with the subject sitting^{1, 2} or standing.³ For this reason, these bizarre ventricular deflections have been ascribed either to a presumed electrical reorientation of the heart resulting from changing contacts between the heart and surrounding intrathoracic tissues^{1, 2} or, in spite of a lack of any correlated measurements to support the contention, to a diminution in coronary flow.³ In any event, in both of these views the basic importance of a concomitant asthenic habitus has been stressed; in the one case because it will allow a greater freedom of cardiac mobility,^{1, 2} and in the other because a congenitally small heart, which supposedly cannot maintain an effective coronary circulation during the readjustments to postural change, is always assumed to be associated with such a body build.³ However, since neither of these interpretations could be reconciled with the occurrence of similar alterations in the electrocardiograms of persons with functional derangements of the cardiovascular system when the record is made with the subject recumbent,^{4, 5} the authors undertook to explore other possible mechanisms which could account for these T-wave changes. The observations of Ewert⁶ and others,^{7, 8} which indicated that augmented adrenergic activity can be responsible for orthostatic T-wave modifications in Leads II and III in persons subject to syncope, suggested that a disturbance of normal vagosympathetic relationships might equally well be applied to explain, in cases of functional heart disease, comparable changes in records made with the subject standing, sitting, or recumbent. This consideration prompted a series of experiments by us in a group of patients with neurocirculatory asthenia. This report presents the results of such studies.

MATERIAL AND METHOD

Among a group of men originally referred to the hospital for a cardiovascular survey because of physical signs and/or symptoms suggestive of structural cardiac disease, 25 patients were selected for more detailed study because their electrocardiograms revealed T-wave changes in Leads II and III

The most significant finding in our present study was the persistence of the electrocardiographic abnormalities after bilateral vagotomy. It should be emphasized that our results are entirely unambiguous in this respect and therefore are against the view that any of the cardiac changes and the fatal outcome of pulmonary embolism are to be attributed to the hypothetical pulmonic coronary reflex over the vagus nerves. The dynamic explanation for cardiac embarrassment and coronary insufficiency which we have suggested in previous work^{7, 10} and summarized elsewhere¹³ will adequately account for the experimental and clinical findings in pulmonary embolism.

Even a dynamic cause of coronary insufficiency, however, does not preclude the advantageous use of coronary vasodilator drugs in pulmonary embolism as these would be indicated in any case of relative coronary insufficiency regardless of origin. It is problematic, as stated before, whether atropine has such a dilator action. However, if atropine is effective in pulmonary embolism it must act upon some mechanism other than the coronary vessels.

CONCLUSION

Experimental studies upon pulmonary embolism have revealed that bilateral cervical vagotomy does not abolish the electrocardiographic alteration produced by the emboli. Pulmonary emboli produce electrocardiographic changes in bilateral vagotomized animals that are similar to the changes produced by pulmonary emboli in nonvagotomized dogs.

These results indicate that there is no ground for the assumption of a vagal pulmonic coronary constriction reflex in pulmonary embolism.

Alternative dynamic explanations are adequate to account for the coronary insufficiency encountered in pulmonary embolism.

We are indebted to Dr. N. Grossman for assistance with these experiments.

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Of those patients whose records showed orthostatic T-wave distortions in Leads II and III, several were selected for an experiment in which the electrocardiographic changes which followed the Flack test could be observed. In the performance of this type of experiment, a continuous record of Lead II was obtained with the subject recumbent just prior to and during a period of forced expiration. The expiratory blast was maintained to the point of obliteration of the radial pulse and was of sufficient force to raise and maintain a column of mercury in the sphygmomanometer to a level of 40 millimeters.

In certain other instances in which orthostatic T-wave abnormalities had developed in Leads II and III, comparable records were obtained in the upright position before and after compression of both legs at the mid-thigh level. The compression was accomplished by snugly fitted pneumatic cuffs inflated to a pressure of 300 mm. of mercury and maintained at this level throughout the experiment. The pressure was applied while the patient was supine and after the legs had been elevated for a sufficient length of time to permit the blood in the superficial veins to drain off as much as possible. Localized bulging of the inflated cuff was prevented by the application of an elastic bandage around the cuff before it was inflated. When significant modifications of the orthostatic distortions resulted from this procedure, the experiment was repeated with compression of equivalent degree being applied just above each ankle.

Finally, in certain selected cases, the effects of amyl nitrite and atropine sulfate were tested separately. The electrocardiograms were made with the patient in the recumbent position, and the patient had abstained from tobacco prior to and during the testing period. A control curve having been obtained, the amyl nitrite was administered by inhalation from a freshly broken pearl containing 5 minims of the drug, after which the electrocardiographic effects were recorded in either a single lead or in multiple limb leads during the relatively brief period when flushing of the skin and tachycardia were maximal.*

The atropine sulfate was administered subcutaneously. Records were obtained forty to sixty minutes afterward. The dose employed was usually 2.5 mg.† dissolved in 2 c.c. of sterile water.

ANALYSIS OF DATA

In each of the 25 cases which form the basis for the present study, orthostatic distortions of the T wave accompanied by varying increments in the heart rate, appeared in Leads II and III. In each instance, the orthostatic T-wave abnormality was completely, or almost completely, abolished by the administration of a sympatheticolytic drug (ergotamine tartrate), and in five instances it was considerably modified by compression of the thighs. In 15 of these patients, changes analogous to those which resulted from the assumption

*The vaporized contents of a pearl of amyl nitrite containing 5 minims of the drug will reflexly excite sympathetic activity to a profound degree. These sympathicomimetic effects are maximal within thirty to sixty seconds after the inhalation of that amount of the drug, and completely disappear in two to three minutes.

†Previous trials had indicated that in order to ensure the vagoparetic action from atropine sulfate, the drug must be administered in this large dosage. When given hypodermically, the maximal effect will appear between forty and sixty minutes after its injection.

in the upright position alone or in both the recumbent and upright positions, in spite of the fact that no substantiating evidence of organic heart disease could be established during a suitable period of observation. Such a method of selection therefore excluded from the study those who exhibited any of the following stigmas: persistent elevation of the arterial blood pressure; persistent tachycardia; any type of cardiac arrhythmia other than a sinus arrhythmia; systolic cardiac murmurs which were not significantly modified by heart rate, postural change, and the respiratory phases; orthostatic hypotension; elevated erythrocyte sedimentation rate; an elevated basal metabolic rate; cardiac and/or aortic enlargement as estimated in the teleroentgenogram by generally accepted methods of cardiac mensuration.

The subjects ranged in age from 18 to 35 years. No one body type was consistently encountered; the asthenic, the hypersthenic, and the intermediate body builds occurred with about equal frequency. The presenting symptoms, not all of which appeared in every case, included nervousness, weakness, excessive perspiration, palpitation, dull or sharp left intramammary pain unrelated to exertion and usually associated with hyperesthesia over the precordium; aches in various joints without redness, swelling, or limitation of motion of these structures; dizziness; shortness of breath of the nonhyperventilation type and usually described as "a feeling as though not enough air can get into the lungs."

The cardiovascular apparatus was repeatedly scrutinized by the usual methods of physical examination. In addition, teleroentgenograms of the chest and erythrocyte sedimentation rate determinations were routinely obtained. In many instances the basal metabolic rate also was measured.

The electrocardiographic studies were performed in the following manner: on the day of admission a record, both in the recumbent and in the upright position, was obtained,* after the technician ascertained that the patient had not been smoking for at least thirty minutes prior to the time of the test. The leads employed were the three standard limb leads and precordial leads C₁, and C₂, taken according to the technique recommended by the American Heart Association. The chest position was carefully marked in order to exclude the possibility of malposition of the exploring electrode, a factor which might contribute to distortion of the T wave in the precordial lead. On the following day, a set of tracings was again obtained and immediately inspected by one of us. If T-wave distortions were noted in Leads II and III in these records, electrocardiograms were made thirty and sixty minutes following the intravenous administration of 0.5 mg. of ergotamine tartrate (Gynergen)†; the technician made certain that the subject had abstained from smoking prior to and during the experiment.

*Previous experiments had indicated that the orthostatic effects upon the electrocardiogram which follow an active change of position were no different from those which follow tilting of the subject to an 80-degree angle with the horizontal, provided the patient did not sway excessively after assuming the upright position, and provided a short waiting period of two minutes was employed to allow for vascular readjustments. For this reason, both methods were interchangeably used.

†Previous clinical trials had indicated that the maximal sympathetogenic effects of ergotamine tartrate, when the drug is administered intravenously in a dosage of 0.5 mg., appear between thirty and sixty minutes after the injection and will last ninety minutes after the injection.

due merely to a lengthening of the diastolic period which ensues with a reduction of the heart rate. This view cannot be arbitrarily denied, but it hardly seems applicable in this instance, since the configuration of the T wave in Leads II and III is not significantly modified by atropine sulfate, even though the cardiac acceleration which followed the administration of this vagoparetic drug exceeded that which resulted from the assumption of the upright position. An alternative concept, which immediately suggests itself as an explanation of this difference, is the possibility that an augmentation of sympathetic activity, physiologically provoked either by the assumption of the upright position or the administration of a vagoparetic drug, can accelerate the sinus rate (chronotropic effect) and independently modify the events associated with electrical systole (dromotropic effect).

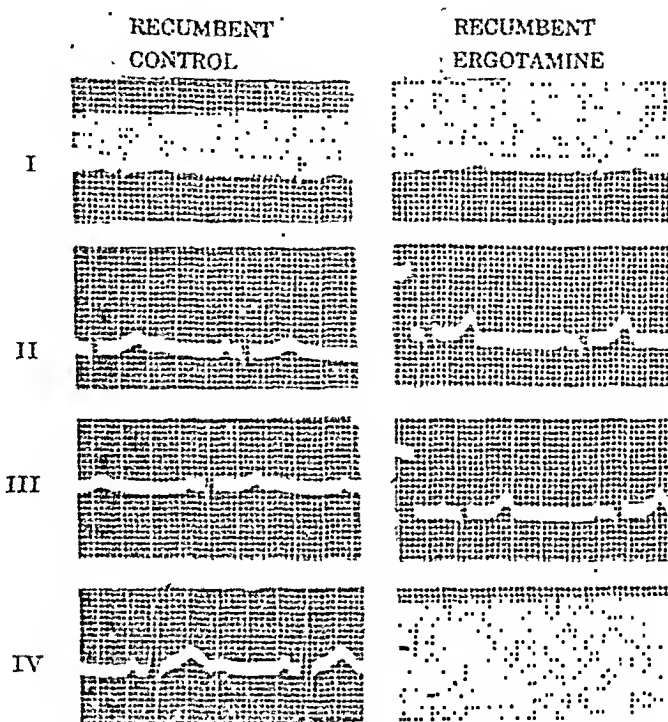


Fig. 2.—Case 3. The electrocardiogram is discussed in the text.

Following the administration of a sympathicolytic drug, such a distinction can apparently be made in some instances, the form of the T wave becoming modified without any significant change in the heart rate (Fig. 2). Therefore, the normalization of the ventricular deflection by ergotamine tartrate, when the electrocardiogram was made with the subject standing, might be ascribed not only to the decrement in the standing heart rate, but also to an inhibition by this drug of a dromotropic sympathetomimetic effect reflexly provoked by the upright position. In addition, this response of the T waves to the administration of ergotamine tartrate would seem to exclude a change in cardiac rotation as being responsible for the original orthostatic aberrations of the ventricular deflections.

CASE 2.—1. The maneuver of tilting the body upright to approximately 80 degrees did not result in a distortion of the T wave in Leads II and III unless a significant cardiac acceleration also developed (Fig. 3).

2. A sympathicolytic drug (ergotamine tartrate) prevented any significant orthostatic cardiac acceleration and also any orthostatic T-wave distortions (Fig. 3).

3. In the electrocardiogram made with the subject recumbent, T-wave changes in Leads II and III were provoked by the administration of amyl nitrite or atropine sulfate. These changes were of the same nature, if not necessarily of the same degree, as those which followed the assumption of the vertical stance (Fig. 3).

Comment.—The facts that orthostatic distortions of the T waves in Leads II and III occur only in association with cardiac acceleration and that such distortions can be prevented

of the upright position were provoked by a sympatheticomimetic drug (amyl nitrite) in the electrocardiogram made with the subject recumbent. In 10 instances, the T wave in Leads II and III of the electrocardiogram made in recumbency underwent varying degrees of modification following the administration of a vagoparetic drug (atropine sulfate). A similar effect followed the Flack maneuver in six instances. The data from five representative cases which have been selected for more detailed analysis will be separately reviewed.

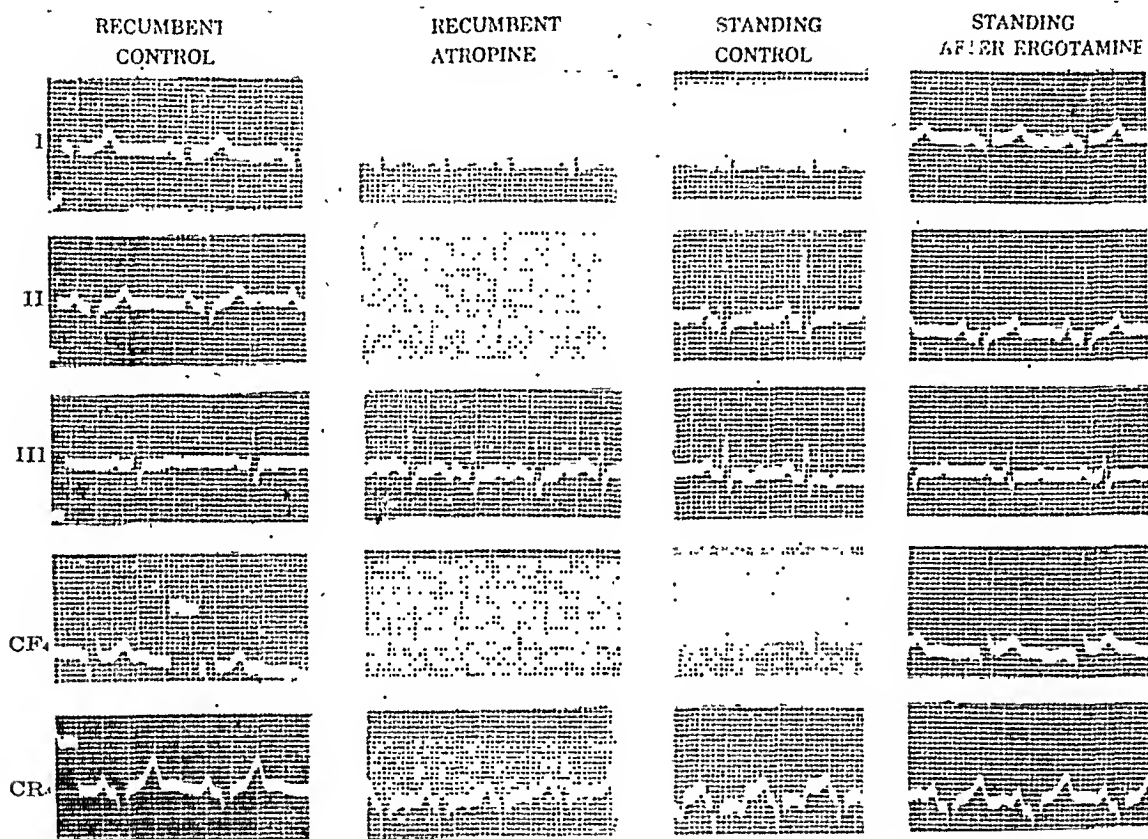


Fig. 1.—Case 1. The electrocardiogram is discussed in the text.

CASE 1.—1. Although the orthostatic T-wave distortions in Leads II and III were associated with some cardiac acceleration, an associated orthostatic tachycardia, in the strictest sense, had not developed. The heart rate with the patient in the recumbent position averaged 70 per minute and, in the upright position, 95 per minute (Fig. 1).

2. Although the heart rate with the patient in the recumbent position became more rapid after the administration of a vagoparetic drug than it had following the assumption of the upright position alone, significant T-wave distortions in Leads II and III developed only during the period of standing. On the other hand, the T-wave distortions in the precordial leads which developed in recumbency after atropine sulfate, and in the upright position before the drug was given, were comparable (Fig. 1).

3. A sympathetolytic drug (ergotamine tartrate) prevented orthostatic cardiac acceleration and also orthostatic T-wave distortions (Fig. 1).

Comment.—The orthostatic T-wave distortions in Leads II and III might conceivably be related to a shortening of the diastolic period which inevitably supervenes with an acceleration of the heart. Conversely, then, the prevention by means of ergotamine tartrate of these orthostatic effects upon the ventricular deflection might be presumed to be

against the opinion that increased cardiac mobility is responsible for orthostatic distortions of the ventricular deflections.

The likelihood that the original orthostatic distortions of the T wave are to be ascribed to impaired coronary flow would seem to be excluded by the normalizing effect of ergotamine tartrate since this drug is believed to produce also some constriction of the coronary arteries. Too, the marked distortion of the T wave in Leads II and III which followed the administration of a profound coronary dilator such as amyl nitrite indicates that a reduction in coronary flow is not a valid concept in attempting to explain T-wave changes which may occur in cases of neurocirculatory asthenia.

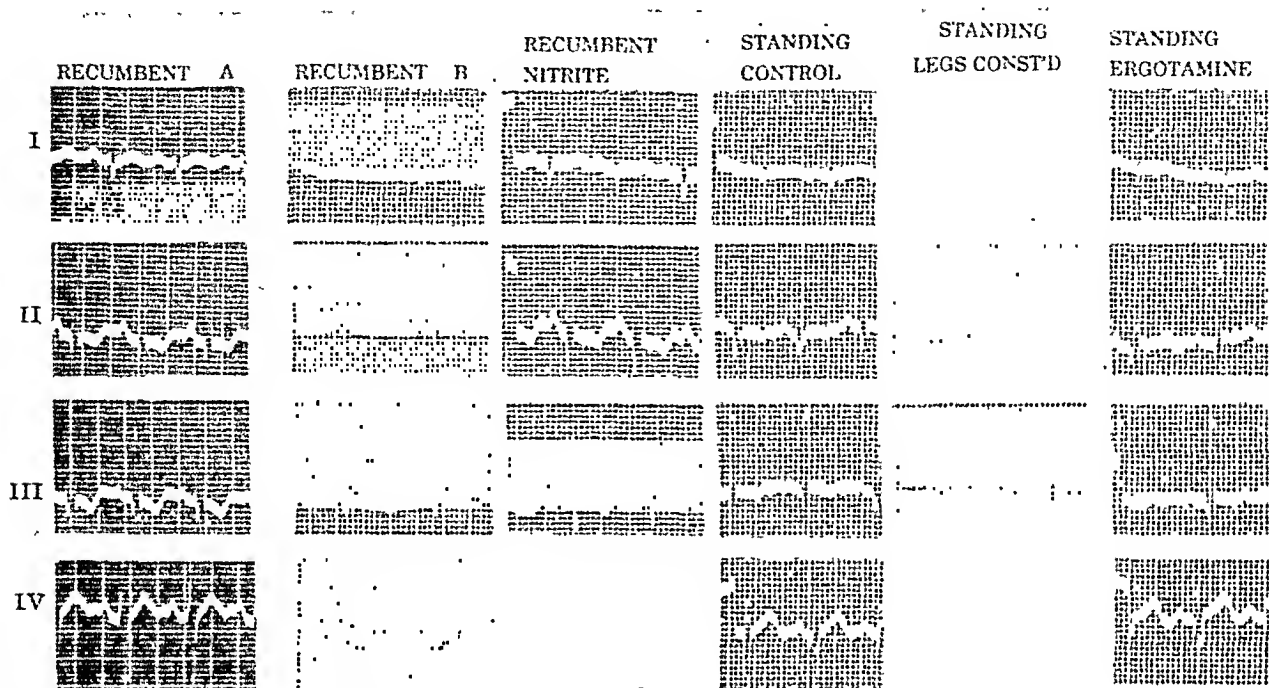


Fig. 4.—Case 3. The electrocardiogram is discussed in the text.

CASE 3.—1. During a febrile period, the electrocardiogram made with the subject recumbent revealed the presence of a sinus tachycardia with a heart rate of 130 per minute and concomitant inversion of the T wave in Leads II and III (Fig. 4).

2. During an afebrile period, the electrocardiogram made with the subject recumbent revealed the presence of a sinus rate of 60 per minute and T waves in Leads II and III of normal amplitude and configuration (Fig. 4).

3. Distortions of the T wave in Leads II and III occurred when the electrocardiogram was made with the subject recumbent, immediately following the inhalation of amyl nitrite. These changes in the ventricular deflection were associated with an increase in the sinus rate to 125 per minute (Fig. 4).

4. Distortions of the T wave in Leads II and III followed the assumption of the upright position alone. These changes in the ventricular deflection were associated with an equally significant increment in the heart rate and were abolished either by constriction of the thighs or by the administration of ergotamine tartrate, both of which procedures resulted in a reduction in the orthostatic heart rate to approximately 100 beats per minute (Fig. 4).

Comment.—In records made with the subject recumbent, T wave distortions in Leads II and III occurred spontaneously during a febrile period or were provoked, when no fever was present, by the inhalation of amyl nitrite. Since these changes are analogous to those which followed the assumption of the upright position, the possibility is suggested that a similar mechanism is operative in these modifications of the ventricular deflections. Inasmuch as cardiac acceleration is a concomitant occurrence in all these circumstances, it might be presumed that the tachycardia alone, with its resultant shortening of the diastolic period, might be the factor responsible for the altered shape of the T wave.

by the use of a sympatheticolytic drug which also reduces the heart rate suggest that the abnormal form of the T wave is related either to the shortened diastolic period which results from the cardiac acceleration or to a mechanism which can provoke a sinus tachycardia as well as independently modify the events associated with electrical systole. The interpretation that the bizarre T wave is related to the increased heart rate per se would seem to be supported by the fact that, following the administration of amyl nitrite, changes identical with the orthostatic distortions occur in records made with the subject recumbent, provided that a comparable acceleration of the rate is provoked by this drug. On the other hand, the fact that the administration of atropine sulfate and of amyl nitrite produce

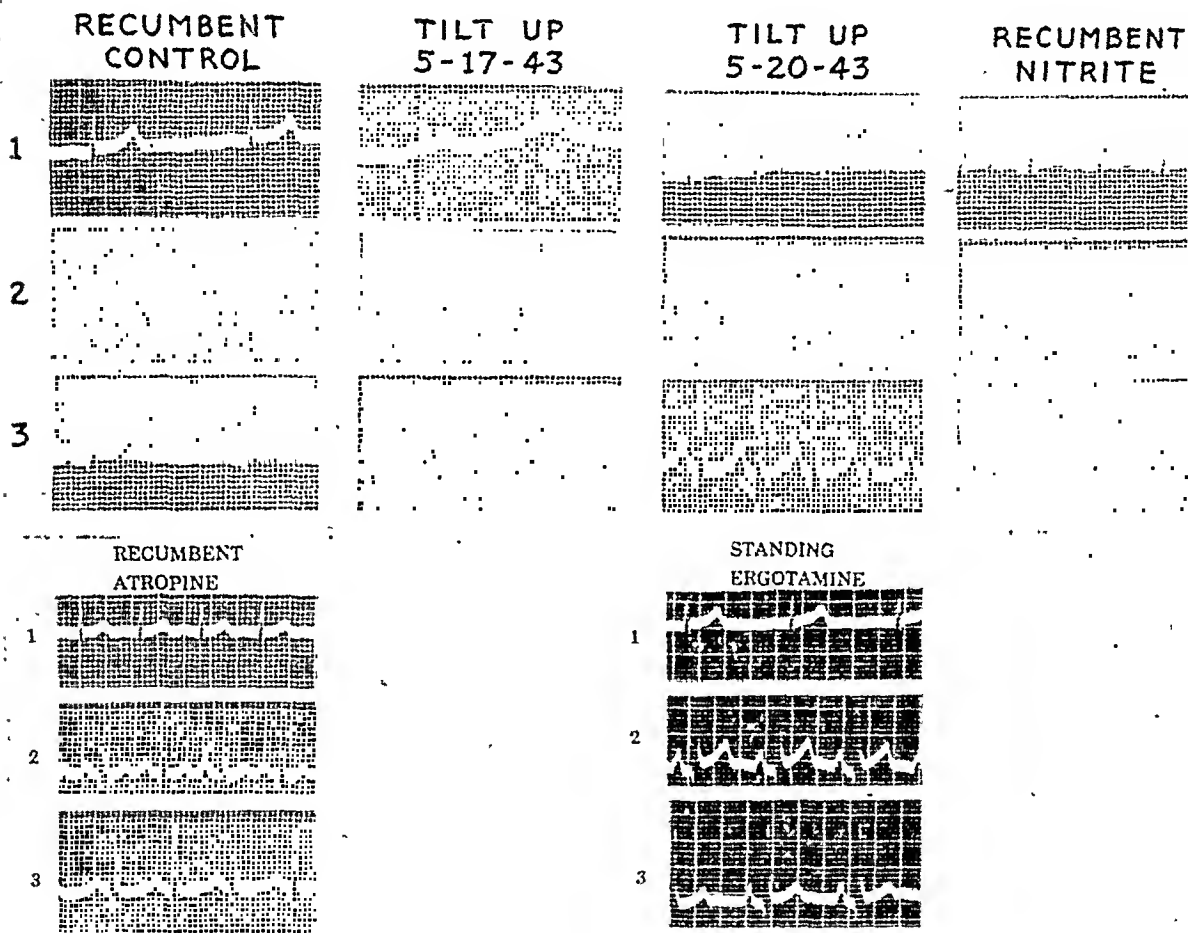


Fig. 3.—Case 2. The electrocardiogram is discussed in the text.

unequal degrees of T-wave modification, even though the tachycardia produced by these drugs is identical, would suggest that the tachycardia and the orthostatic T-wave changes represent separate chronotropic and dromotropic actions, respectively, of a sympathetico-mimetic effect. The differing dromotropic influences of atropine sulfate and amyl nitrite, in turn, can be predicated upon the fact that the latter drug is the more profound adrenergic stimulant in man.⁵ The orthostatic distortions of the T wave which develop in Leads II and III when there is an associated orthostatic tachycardia presumably are also an electrocardiographic expression of the dromotropic effect of heightened sympathetic activity, since they do not appear when the heart is under the influence of a sympatheticolytic drug such as ergotamine tartrate. Also, this modifying influence of ergotamine tartrate, as well as the lack of any significant T-wave change when the upright position is unassociated with any significant cardiac acceleration, are undoubtedly strong evidence

siderably more bizarre, but these changes in the ventricular deflection were associated with a more significant cardiac acceleration (Fig. 5).

3. In the electrocardiogram made with the subject in the upright position after compression of the thighs, the T waves in Leads CF₁ and CR₁ (which were the only leads available for inspection) reverted to a positive deflection. This change in the T wave was associated with a decrement in the heart rate of only 12 beats per minute (Fig. 5).

Comment.—Although orthostatic T-wave distortions in the limb leads developed in association with a moderate degree of cardiac acceleration, even more profound changes in the ventricular deflection were seen when the electrocardiogram was made with the subject recumbent, after the administration of atropine sulfate. Obviously, the disparity is not to be related to differences in cardiac rotation, since the ventricular deflections in the precordial leads in the orthostatic electrocardiogram were normalized merely by a maneuver (compression of the thighs), which could not possibly influence the position of the heart within the chest. It must therefore be concluded that the configuration of the T wave is related to the heart rate in one of two ways: first, that the more rapid the rate, the shorter the diastolic period and hence the more abnormal the T wave, or, second, that the increase in rate and the T-wave changes are separate chronotropic and dromotropic effects, respectively, of heightened sympathetic activity. The first interpretation does not seem to be applicable, since, in this instance, the orthostatic T-wave distortions were associated with a heart rate of less than 100 per minute, which was hardly sufficiently high to shorten the diastolic period enough to distort the T waves.

CASE 5.—1. On the day of admission, in the routine tracing obtained in the recumbent position, there was a sinus tachycardia with a heart rate of 140. The T waves were considerably distorted in Leads II and III (Fig. 6).

2. On the following day, in the recumbent position, the tachycardia had disappeared and the T waves were normal (Fig. 6).

3. Distortions of the T waves in Leads II and III, identical with those which were evident in the recumbent electrocardiogram on the day of admission, were provoked by the upright position even though the degree of cardiac acceleration was much less pronounced (Fig. 6).

4. The orthostatic distortions were prevented by a sympathetolytic drug, such as ergotamine tartrate. This prevention of the orthostatic T-wave distortions was associated with some retardation of the orthostatic cardiac acceleration (Fig. 6).

5. A vagoparetic drug such as atropine sulfate produced in the recumbent electrocardiogram distortions of the T waves in Leads II and III which are comparable to those which resulted from the upright position (Fig. 7).

6. The orthostatic T-wave distortions in Leads II and III were also abolished in large part by constriction of the thighs. This effect was also associated with a retardation of the orthostatic acceleration of the heart (Fig. 7).

7. A sympathetomimetic drug, such as amyl nitrite, produced in recumbency, some cardiac acceleration and inverted the T waves in Lead II to the same extent as did a vagoparetic drug or the assumption of the upright position (Fig. 7).

8. The Flack maneuver, in recumbency, was followed by an inversion of the T wave in Lead II, resembling the distortion of this deflection which is produced by a sympathetomimetic drug such as amyl nitrite, by a vagoparetic drug such as atropine sulfate, or by the assumption of the upright position (Fig. 7).

Comment.—It is evident that in this case cardiac acceleration was constantly an associated feature in those electrocardiograms in which abnormal T waves appeared in Leads II and III. For this reason, the bizarre T waves would seem to be related to the tachycardia with its resultant shortening of the diastolic period. This view seems to be supported by the fact that the orthostatic distortions of the T wave are abolished when the heart rate in the upright position is reduced by a sympathetolytic drug or by compres-

On the other hand, it seems to be equally plausible to relate both the tachycardia and the bizarre T waves to the separate chronotropic and dromotropic effects, respectively, of heightened sympathetic activity provoked either by the fever, the amyl nitrite, or the vertical stance. In this particular case, such an interpretation is especially applicable, since on another occasion, in a record made with the subject recumbent, the administration of a sympathetolytic drug was followed by a significant modification in the T waves without any alteration of the heart rate (Fig. 2). It is also noteworthy that either ergotamine tartrate or constriction of the thighs considerably modified the orthostatic distortion of the T waves in Leads II and III. Although this effect was presumably achieved by these procedures because of their inhibitory influences upon reflex sympathetic excitation, the mode of action is undoubtedly dissimilar. In the former instance a pharmacologic barrier between sympathetic fibers and end organs in the heart was created, whereas the other maneuver acted to improve venous return, thereby diminishing the intensity of reflex adrenergic activity.

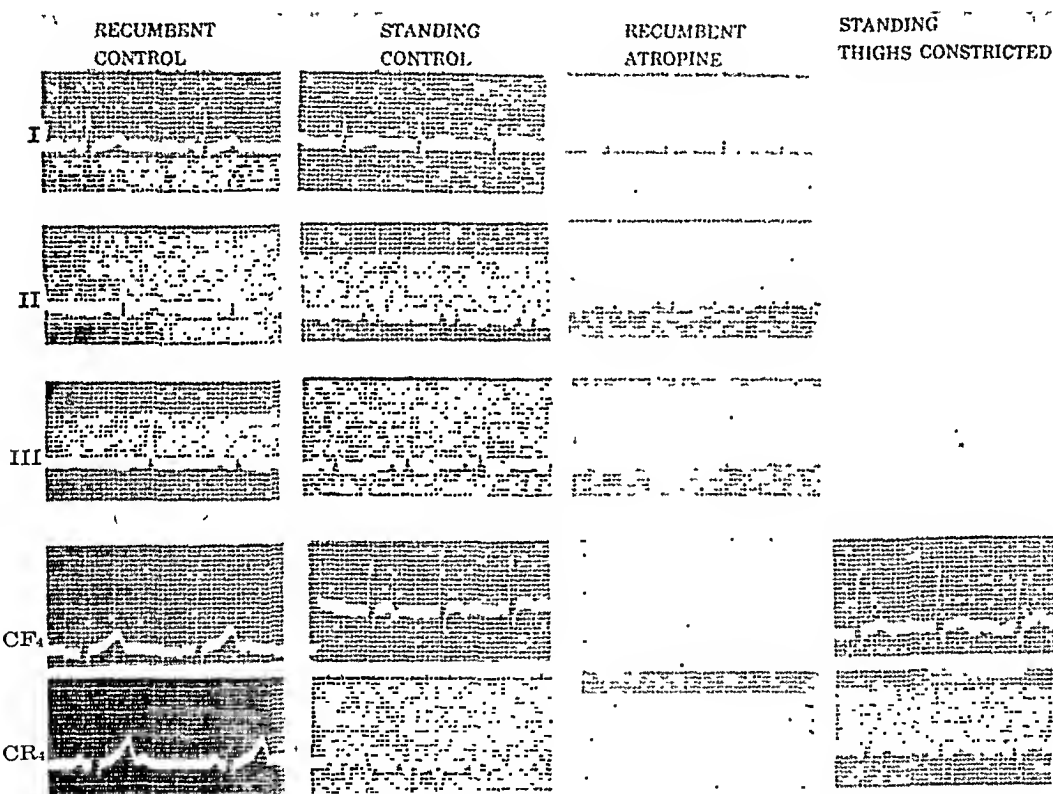


Fig. 5.—Case 4. The electrocardiogram is discussed in the text.

In this case, too, cardiac mobility must be dismissed as a cause for the original orthostatic aberrations of the ventricular deflection. Otherwise, the correction of the orthostatic distortions of the T wave by ergotamine tartrate or compression of the thighs would be difficult to explain.

CASE 4.—1. Moderately pronounced orthostatic distortions of the T waves in limb leads II and III and in precordial leads CF_4 and CR_4 developed, in association with some cardiac acceleration, although a true orthostatic tachycardia did not occur. The heart rate in recumbency was approximately 60 beats per minute and in the upright position approximately 95 beats per minute (Fig. 5).

2. In the electrocardiogram made with the subject recumbent, after the administration of a vagoparetic drug such as atropine sulfate, the T wave in all leads became con-

sion of the thighs. On the other hand, the Flack test, which is known to reflexly excite adrenergic activity by diminishing venous return,⁹ inverts the T wave without accelerating the rate (Fig. 7). This might imply that an augmented sinus rate and a concomitant T-wave distortion can be considered separate chronotropic and dromotropic effects, respectively, of heightened sympathetic activity, and that the two need not necessarily always act in combination to the same degree. In extension of this concept, the salutary effect of a sympathetolytic drug or of compression of the thighs on the orthostatic T-wave distortions would be interpreted to indicate that both of these procedures have inhibited, in a selective manner, both the chronotropic and dromotropic effects of heightened sympathetic activity provoked by the upright position.

The remarks which have been incorporated in the discussion of the previous cases, concerning the possible relationship between cardiac mobility or impaired coronary flow and the orthostatic T-wave distortions, apply also to this case.

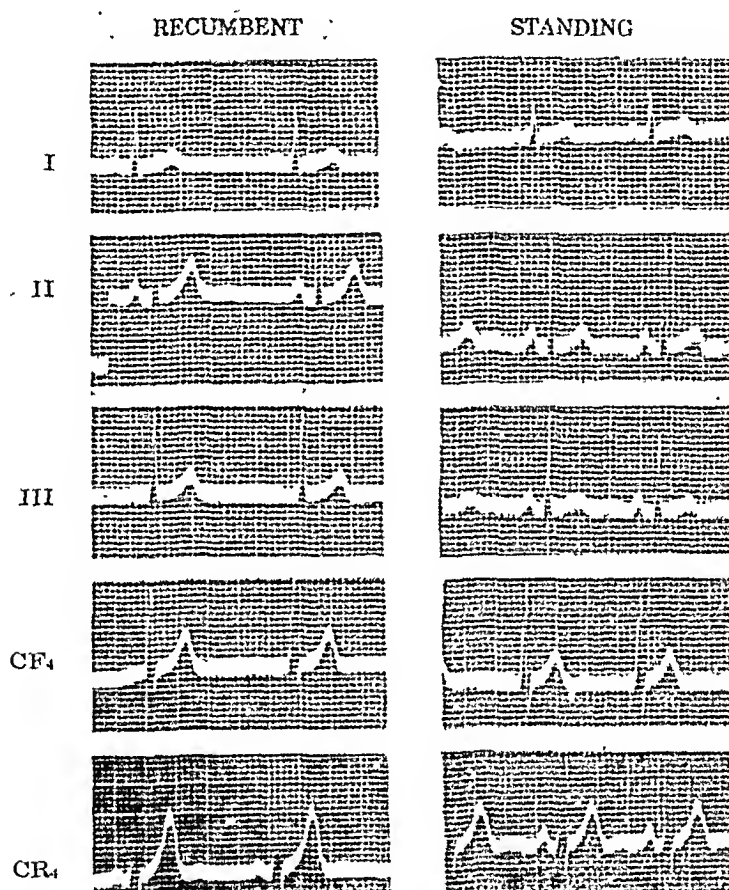


Fig. 8.—For description, see text.

DISCUSSION

Although we have presented evidence which seems to refute the interpretation that a change in cardiac rotation^{1, 2} or a diminution in coronary flow³ is chiefly responsible for the T-wave distortions which develop in Leads II and III when an electrocardiogram is made with the subject standing, it is not the intent of this report to discredit the practice of obtaining orthostatic records in cases of neurocirculatory asthenia. On the contrary, it is considered by us to be a useful procedure in the study of patients with functional cardiovascular disturbances, since such provocative aberrations of the ventricular deflection apparently offer a simple objective method for the recognition of an under-

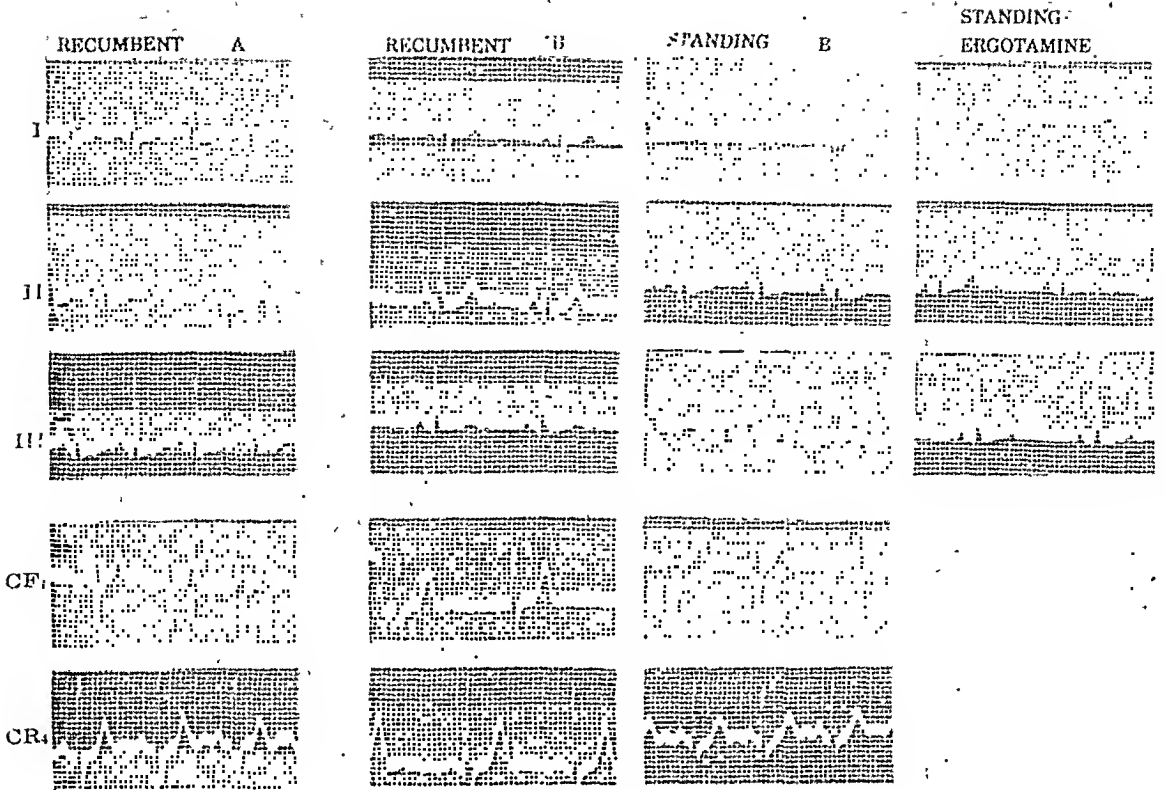


Fig. 6.—Case 5. The electrocardiogram is discussed in the text.

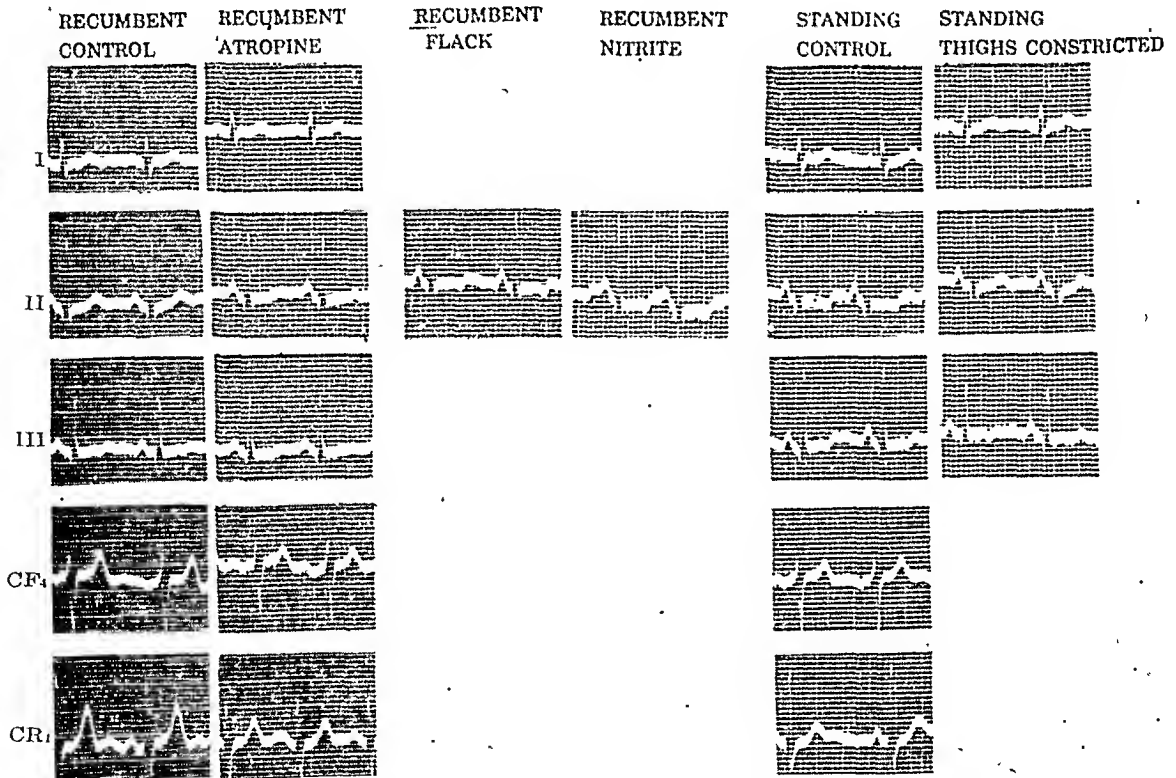


Fig. 7.—Case 5. The electrocardiogram is discussed in the text.

can be utilized to distinguish neurogenic T-wave changes from those due to intrinsic heart disease, and thus provide a means for the proper appraisal of aberrations of the ventricular deflection which occur without any other evidence of structural cardiac disease.

SUMMARY

1. It has been demonstrated, in a study of 25 patients with neurocirculatory asthenia, that heightened sympathetic activity, rather than a change in cardiac rotation or a diminution in coronary flow, is chiefly responsible for abnormalities of the T wave which appear in Leads II and III in electrocardiograms made with the subject recumbent or standing.

2. Since a fundamental component of neurocirculatory asthenia is a disruption of normal vago-sympathetic relationships, it is possible to reconcile with this disorder such "sympatheticogenic" aberrations of the ventricular deflections.

3. The body build does not seem to be the factor responsible for T-wave changes in neurocirculatory asthenia, since such abnormalities have been observed in those of sthenic and asthenic habitus.

4. The experience gained from the present study suggests that the reaction to ergotamine tartrate provides a simple means for differentiating "sympatheticogenic" distortions of the T waves from those due to intrinsic cardiac disease.

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lying vegetative disorder. Support for this view is to be found in the observations of one of us⁵ that, in emotionally stable individuals, even though they are of asthenic habitus, the assumption of the upright position will not induce significant T-wave changes (Fig. 8). Supposedly, in the normal subject, the orthostatic augmentation of sympathetic activity which physiologically develops because of the vascular readjustments which accompany the vertical stance⁹ is not in itself adequate to produce a registrable dromotropic effect upon the events associated with electrical systole, even though a chronotropic effect is evident in the moderate cardiac acceleration which occurs. Orthostatic T-wave distortions in patients with neurocirculatory asthenia are therefore presumed to represent additive sympathetomimetic effects, i.e., reflex adrenergic activity superimposed on a state of autonomic imbalance with sympatheticotonic preponderance. The latter is believed to arise from the anxiety, with its attendant disruption of normal vagosympathetic relationships,

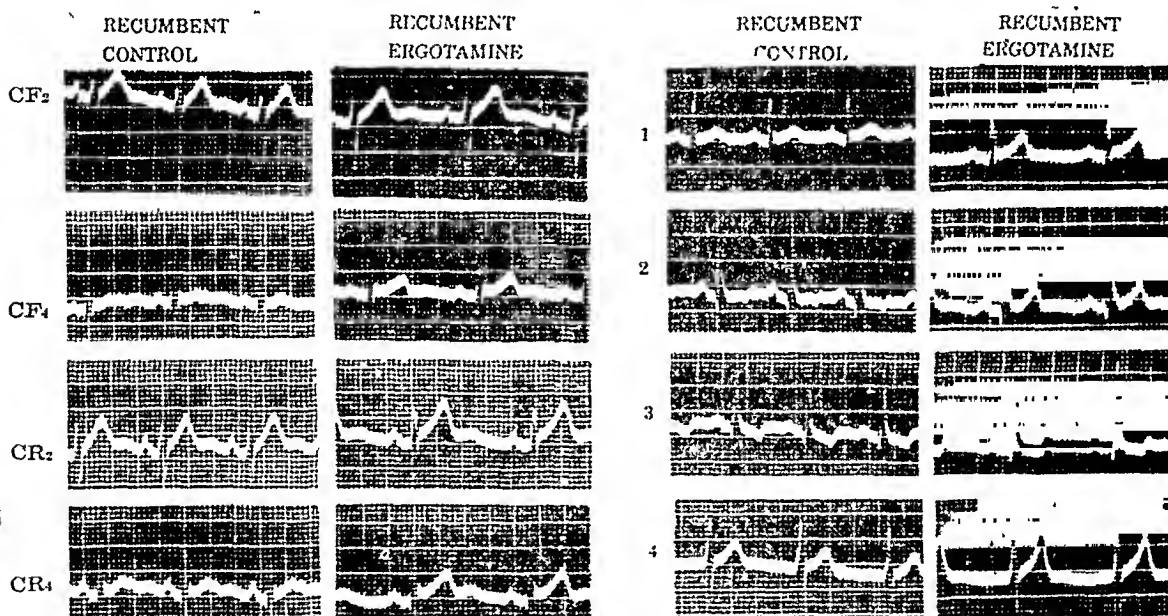


Fig. 9.—For description, see text.

which is recognized to be a fundamental component in the syndrome of functional heart disease.¹⁰ It is also conceivable that, when the dysfunction of the vegetative nervous system is sufficiently profound, the resulting sympathetic overactivity may express itself in much the same manner as it has in the precordial leads in emotionally unstable persons,¹¹ so that spontaneous T-wave aberrations will appear in Leads II and III even when the electrocardiogram is made with the subject recumbent. Actually such changes have been noted, in not a few instances, in cases of neurocirculatory asthenia^{4, 5} and, as in the case of analogous T-wave alterations in the precordial leads,¹¹ the mechanism responsible for them seems to be established from the normalization which follows the administration of a sympathetolytic drug, such as ergotamine tartrate (Fig. 9). Therefore, it would appear that this simple testing method

to bring forward one end of the tongue depressor by means of a wad of paper or cotton. The screen is set vertically close to the body of the patient but not in contact with it. The screen must be free to move laterally, but its distance from the patient must not vary during the observation. The stick is then attached vertically at the center of the screen by a bit of adhesive plaster. If the fluoroscope is used frequently for heart studies it is convenient to have a vertical black line painted on the screen, in place of the stick.

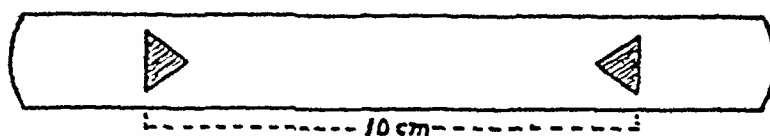


Fig. 1.—Wood tongue depressor with lead triangles attached. The interval between the vertical edges of the triangles measures 10 cm. and is called the "base line."

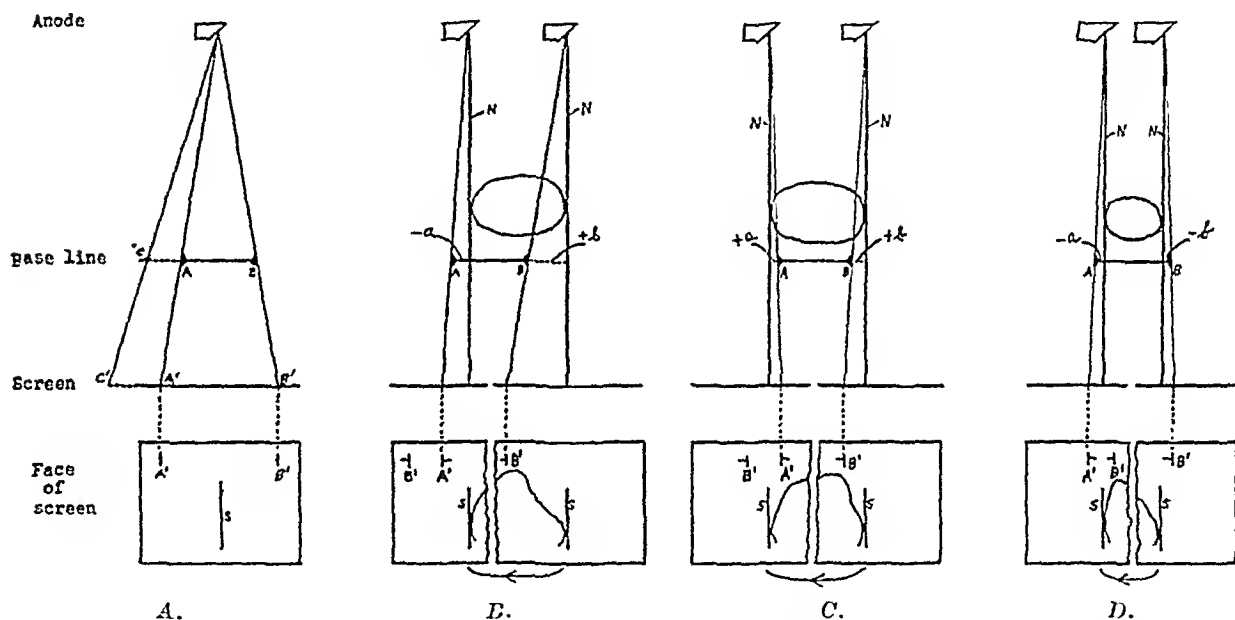


Fig. 2.—Diagrams illustrating the geometric principle on which is based a new method of measuring the transverse diameter of the heart. The upper portion of each diagram represents the relation of the target, heart, base line, and screen, shown in horizontal plan; the lower portion of the diagrams represent the face of the screen, seen in vertical elevation. Letters have significance as follows: *A* and *B*, left- and right-hand lead triangles, 10 cm. apart; the interval, *AB*, is called the "base line." *A'* and *B'*, marks on screen indicating positions of shadows of lead triangles. *a* and *b*, corrections to be added to or subtracted from length of base line. *N*, the line of intersection of the "normal plane" and the plane of the diagram. *S*, the stick attached at the center of the screen. Diagram *A*, The magnification ratio is given by $A'B'$ divided by AB . When this ratio is known any interval on the base line, AB , or on an extension, such as AC , may be calculated readily from the measured length of the similar interval, $A'C'$, on the screen. Diagrams *B*, *C*, and *D* represent different positions and sizes of heart. In each diagram two successive positions of the screen and target are represented. The position to the right precedes that to the left. B' is marked when the screen is in the first position. After the screen is moved to the left A' is added. The interval, $A'B'$, corrected for magnification, is added to, or subtracted from, the length of the base line, AB , to give the transverse diameter of the heart.

When the screen is illuminated the shadows of the lead triangles will appear, lying somewhat above the shadow of the heart and separated by a distance of somewhat more than 10 centimeters. The stick will appear in the midst of the heart shadow but rather nearer to the right border if the patient and the screen have been centered in the usual manner. Unless the screen has an exceptionally long range of lateral motion it now will be necessary, in

A METHOD FOR THE ORTHODIAGRAPHIC MEASUREMENT OF THE TRANSVERSE DIAMETER OF THE HEART BY MEANS OF THE SIMPLE FLUOROSCOPE

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THE transverse diameter of the heart, measured by the orthodiagraphic method, is widely accepted as the most significant measurement upon which to base a judgment of the heart size. This report describes a method by which a true orthodiagraphic measurement of the transverse diameter may be made by means of the ordinary fluoroscope without the standard orthodiagraphic equipment. The principle of the method is simple. If a vertical line, drawn at the center of the screen, is aligned first with one border of the heart shadow and then with the other border, by moving the screen laterally, then the distance through which the screen is moved is equal to the transverse diameter. This is a necessary consequence of the fact that the screen and the tube are rigidly connected and move as a unit. The amount of this lateral movement might be measured by a tape reaching from the screen to a near-by wall or by a plumb-line reaching from the screen down to a scale on a table below the screen. Neither of these methods would be quite convenient in actual practice, but the method now to be described accomplishes the same purpose expeditiously and accurately with the simplest accessories. The actual technique first will be described and then, by means of diagrams, the logic of the procedure will be set forth.

The accessories required are the following:

1. A wood tongue depressor on which are mounted, by means of adhesive plaster, two triangular pieces of lead placed with their vertical sides parallel and exactly 10 cm. apart, with the apices that are opposite the vertical edges pointing toward each other (Fig. 1). The line, 10 cm. long, between the vertical edges will be called the "base line."
2. A thin, straight wood stick, such as an ordinary wood applicator.
3. A grease pencil.
4. A centimeter scale.

PROCEDURE

The patient is placed in the usual position for fluoroscopy and the tongue depressor, with the lead triangles, is attached by adhesive plaster to the anterior chest wall, horizontally and centrally, at about the level of the second costal cartilages. It is necessary that the lead triangles be equidistant from the screen; therefore, if the chest is irregularly shaped, it may be necessary

and the intervals (a and b) between its ends and the normal plane are determined first at the left border of the heart and then at the right border. The magnitudes of these intervals are calculated from the measured corresponding intervals on the screen reduced by division by the previously determined magnification ratio. When the normal plane is placed at the left border of the heart if the right hand shadow lies to the left of the stick then the right end of the base line falls short of the normal plane and the corrected measured interval on the screen is to be added to the length of the base line, whereas if the shadow lies to the right of the stick the right end of the base line reaches beyond the normal plane and the corrected measured interval is to be subtracted from the length of the base line. The same procedure is carried out at the right border of the heart, the left-hand shadow and the left end of the base line being considered. The several possible relations are illustrated in Fig. 2. In B , TD (transverse diameter) $= 10 \text{ cm.} + b - a$; in C , $TD = 10 \text{ cm.} + b + a$; in D , $TD = 10 \text{ cm.} - b - a$. For an understanding of the method it is necessary to see how these end corrections may be calculated and applied, as in these examples, but, fortunately, in practice the two end corrections do not need to be considered separately, for the geometric relations are such that the interval between the two marks, A' and B' , on the screen, when divided by the magnification ratio, is equal to the algebraic sum of the two end corrections. Hence the simple procedure of Step 4 as described previously, is valid and the observer is spared some time and effort. If the TD of the heart is less than 10 cm. this combined correction always is negative, but it is always positive if the TD is greater than 10 centimeters. In the case of a small heart, with a TD near 10 cm., the observer might be in some doubt about the sign of the small correction, but in this case another characteristic of the geometric relations provides the answer; it may be seen from the figures that when the marks "face" each other ($—| |—$) the correction always is positive; when they are turned away from each other ($|— —|$) the correction always is negative.

The geometric principle on which this technique is based is simple and obvious, so that an a priori conviction of the soundness of the method reasonably may be entertained. However, the results given by the method have been compared with measurements obtained in the same cases by the use of standard orthodiagraphic equipment. The discrepancies in the results, a few millimeters at the most, can be explained fully by some uncertainty about the exact location of the border of the heart's shadow. Obviously this uncertainty affects the standard orthodiagraphic method as much as it does the method here described.

In practice, this new method has been found simple and expeditious. Although the explanation of the procedure may give the impression of complexity, the fact is that after a few repetitions the steps seem obvious and are easily remembered. Equipped with this method a clinician who has only a simple fluoroscope is enabled to measure the most significant dimension of the heart with satisfactory accuracy and can thus estimate the heart's size and follow the changes in size during treatment.

most cases, to have the patient move a little to his right until the stick appears to lie at about the center of the transverse diameter of the heart shadow. Thereafter the patient should remain immobile.

The remainder of the procedure will be described as comprising four steps.

Step 1.—(Fig. 2, *A*.) The upper angles of the shadows (*A'* and *B'*) of the lead triangles are marked on the screen with the grease pencil. The distance in centimeters between these marks, to be measured after the whole observation has been completed, divided by 10, gives the "magnification ratio," a number that is to be used as a correction to later measurements.

Step 2.—(Fig. 2, *B*.) The screen, with the tube, is moved to the observer's right until the stick appears tangent to the left border of the heart shadow. Then the lower angle of the shadow (*B'*) of the right-hand* triangle (*B*) is marked on the screen, using a short vertical line drawn downward from the angle and a short horizontal line indicating the direction of the apex of the triangle. The mark then will appear as a letter T placed on its side; thus, —|.

Step 3.—(Fig. 2, *B*.) The screen is moved to the observer's left until the stick appears tangent to the right border of the heart shadow. The lower angle of the shadow (*A'*) of the left-hand triangle (*A*) is marked on the screen, using the same symbol as that for Step 2, but reversed; thus |—.

Step 4.—(Fig. 2, *B*.) The interval between the two marks (—| and |—) now is measured. This measurement is divided by the magnification ratio and the quotient is added to 10 centimeters. The sum is equal to the transverse diameter of the heart.

DISCUSSION

A vertical plane passed through the target and the stick is approximately perpendicular to the screen. The plane, when placed tangent to one heart border, is parallel to its position when placed tangent to the other border. If the plane is nearly perpendicular to the screen the distance between its two positions, when placed tangent to the two heart borders in succession, is equal to the true radiologic "transverse diameter" of the heart. In what follows, the plane will be called the "normal plane," whether placed at the right border of the heart or at the left border.

The base line defined by the two lead triangles on the anterior surface of the chest is a device for measuring the interval between the two positions of the normal plane when the latter is placed in succession at the left and the right border of the heart. The method may be compared to the measurement of an object, for example the top of a desk, by means of an ungraduated, 5-foot pole together with a graduated foot rule. Neither end of the pole need be aligned exactly with the edge of the desk top; the extent to which it extends beyond or falls short can be measured by the foot rule and the intervals added to or subtracted from 5 feet. The diagrams in Fig. 2 show the application of this principle to the fluoroscopic problem. The base line on the chest remains fixed

*The words "right" and "left" are used to signify direction relative to the observer, except where the reference is to a border of the heart; in the latter case the words are used with the usual anatomic significance.

patients when the splanchnic nerves were sectioned with the objective of lowering the blood pressure. Such observations form the subject of this paper. In the earlier part of these studies the sub- and supradiaphragmatic resection of the greater, lesser, and least splanchnic nerves on both sides was done in succession at ten-day to two-week intervals.⁴ In the later operations, done after 1940, the Smithwick operation was carried out.^{14, 15} In this operation there is bilateral removal of the entire great splanchnic nerve with division of all of its aortic branches coupled with interruption of the communicating rami of the ninth to the twelfth dorsal segments, inclusive, and the first and second lumbar ganglia, together with excision of the sympathetic trunk over this area. The two sides are operated upon at ten-day to two-week intervals. The splanchnic bed is the mechanism of the human organism for maintaining the level of blood pressure essentially constant in changing from sitting to lying and standing position, and removal of the sympathetic impulses affecting the caliber of this bed has been found to give, in certain instances, a reduction of elevated blood pressure to normal levels, regression of retinal changes, and a disappearance of symptoms which were associated with hypertension.

Since 1939, observations have been made on 7 patients before and after the less complete operation of splanchnic resection, and on 19 patients before and after the Smithwick operation. The surgical aspects of these studies will be reported elsewhere.²¹

METHODS

The peripheral blood flow was measured by our modification^{25, 26} of the method of Hardy and Soderstrom.²⁷ The methods used were described in the earlier paper¹ and need not be repeated. Peripheral blood flow was expressed as cubic centimeters per square meter per minute. In the course of the observations records were made of rectal temperature and of the temperatures of eleven areas on the anterior surface of the body (Fig. 1) from which the average weighted skin temperature could be estimated, of basal metabolic rate, of blood pressure, and of heart rate.

Plan of Procedure.—The plan of making the measurements of peripheral blood flow was described in a preceding paper.¹ All measurements were made with the patients in a basal metabolic state. The peripheral blood flow was measured on one or more occasions to secure control or preoperative levels of peripheral blood flow and of the other data. Shortly afterward the splanchnic nerves were sectioned on one side. When the patient had recovered from this procedure ten to fourteen days later, the observations relating to peripheral blood flow were repeated, after which the splanchnic nerves on the other side were sectioned. Ten days to two weeks later still, the observations relating to peripheral blood flow were repeated as well as at longer intervals after the completed operation. When patients returned for observations after discharge from the hospital, they were hospitalized overnight in order to be kept in a basal state

*The earlier operations were done by Dr. Frank Glenn and the later ones by Dr. Bronson Ray. We wish to thank these members of the Department of Surgery for their cooperation in making these studies possible.

THE EFFECT OF SPLANCHNIC RESECTION ON THE PERIPHERAL BLOOD FLOW AND RECTAL AND SKIN TEMPERATURES IN HYPERTENSION

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IN A PRECEDING paper we have described observations relating to the peripheral blood flow and skin and rectal temperatures in patients with essential hypertension.¹ In those studies we found that the peripheral blood flow was decreased in persons with essential hypertension as compared with normal young subjects, that the rectal temperature was higher in hypertension, but the average weighted skin temperature was lower in subjects with hypertension than in normal subjects. Moreover, roughly speaking, the upper part of the body was warmer and the lower part colder in hypertension than in normal subjects indicating a greater blood flow in the upper part of the body and a lesser peripheral blood flow in the lower part of the body in hypertensive patients. There are, then, fundamental differences in the distribution of blood to the periphery in hypertensive patients as compared with normal subjects, and as compared with patients exhibiting hypertension as a part of coarctation of the aorta² and pheochromocytoma.³

The medical treatment of hypertension has neither yielded results which were uniformly successful nor has it significantly altered the natural history of the disease (Stewart⁴ and Atchley⁵). As a consequence there have come in rapid succession in recent years the attempts to lower blood pressure in arterial hypertension by surgical procedures designed to interrupt sympathetic nerve pathways. At first partial sympathectomy was done (Craig and Brown⁶ and Craig⁷). Then anterior nerve root section was carried out (Adson and Brown,⁸ Adson,⁹ Heuer,¹⁰ and Page and Heuer^{11, 12}). Then followed in succession the attempts to interrupt the sympathetic nerves more completely (Allen and Adson,¹³ Smithwick,^{14, 15} Peet, Woods, and Braden,¹⁶ Peet and Woods,¹⁷ and Grimson^{18, 19}). Since then additional reports have been made by other observers.²⁰⁻²⁴ A fall in blood pressure is achieved by these surgical measures in a certain number of subjects. It appears that the so-called Smithwick procedure^{14, 15} is one of the most effective.

Since the peripheral blood flow in hypertensive patients shows certain differences from normal individuals we wished to see how the peripheral blood flow and rectal and skin temperatures were altered in these same hypertensive

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Those having the partial operation are separated in Table I from those in whom the Smithwick procedure was done. Moreover, since the object of the surgical procedure was to lower the blood pressure, the patients were grouped into those in whom the blood pressure fell to normal after operation, those in whom the blood pressure fell moderately, and those in whom the blood pressure was unaffected by operation. This was done in order to ascertain whether any changes in the peripheral blood flow and skin and rectal temperatures were brought about in these respective groups as a result of the surgical procedure.

OBSERVATIONS

Observations Relating to Those Patients Subjected to the Smithwick Procedure in Whom the Blood Pressure Fell to Normal Limits.—In seven patients, six women and one man, the blood pressure fell to normal following the Smithwick operation. In them we have compared the preoperative measurements of the circulation with those made when the blood pressure after operation was at normal levels. The average of the blood pressure for the group was 178/120 before and 124/89 after operation. The average rectal temperature, which was 37.54° C. before operation, that is to say higher than normal²⁸ (Table I, Fig. 1), fell to 37.01° C., but still remained higher than normal. The average weighted skin temperature which was 33.86° C. before operation fell to 33.49° C., that is to say below normal. While these were the trends with respect to rectal and average weighted skin temperatures, statistical analysis showed that they were probably not significant changes. The temperature for areas of the upper part of the body fell as compared with the preoperative levels. These areas were: Areas 1 to 6 and included the forehead (Area 1), the upper chest (Area 2), the lower chest (Area 3), the abdomen (Area 4), the upper arm (Area 5), and the forearm (Area 6). The temperatures of the upper (Area 8) and lower thigh (Area 9) were essentially unchanged by the operation but the temperature of the leg (Area 10) and of the foot (Area 11) *increased* very much; the rise in temperature in the latter was 2.2° C. The greatest fall in temperature after operation, namely 1° C., was in the upper arm (Area 5) and forearm (Area 6). The changes in temperature in these areas were consistently in this direction. The greatest rise in temperature, namely 2.2° C., occurred in the foot (Area 11); on statistical analysis this is slightly significant. There was fall in the average peripheral blood flow from 69 c.e. per square meter per minute to 50 c.e. per square meter per minute. The blood flow, however, varies considerably in individual patients; in some patients the peripheral blood flow increased after operation, while in others it decreased. The change is not significant. The basal metabolic rate before operation averaged +3 per cent and after operation, -7 per cent.

Observations Relating to Those Patients Subjected to the Smithwick Procedure in Whom Blood Pressure Decreased Moderately but Did Not Reach Normal.—Seven patients, three men and four women, were in this group (Table I, Fig. 2). The average of the blood pressures before operation was 213/125 and after operation it was 182/112. After operation the rectal temperature was essentially unchanged. The average skin temperature for all the individual

for the observations the next morning. Occasionally, if patients lived near by, they came to the hospital by taxi early in the morning before breakfast and rested sufficiently long to insure basal conditions. All observations were made at

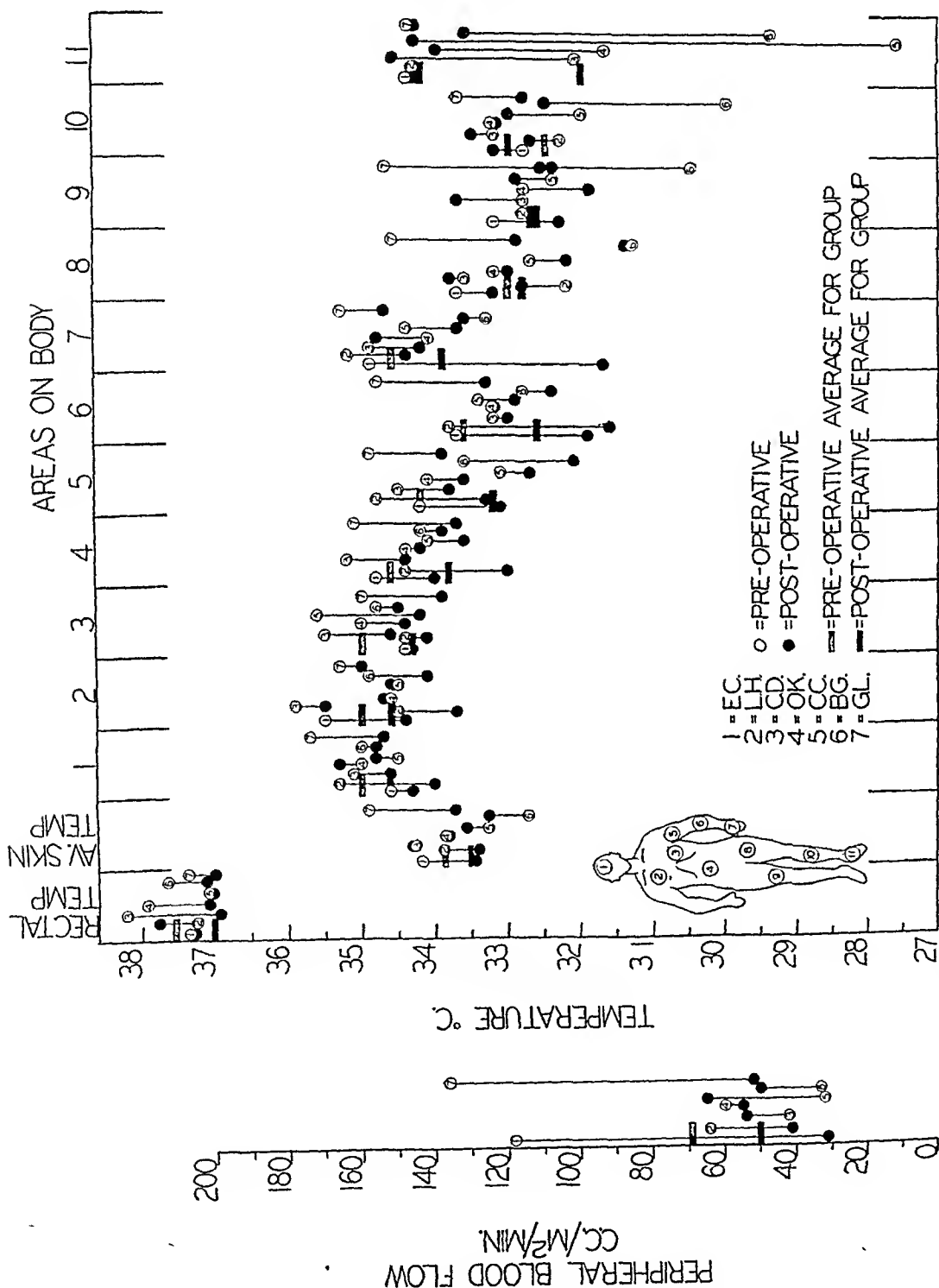


Fig. 1.—In this figure are shown data relating to patients with hypertension who had the Smithwick operation, and in whom the blood pressure fell to normal after operation (Table I). The numbers in the open circles in the chart refer to the patients indicated. The open circles refer to measurements made before operation, and the closed circles refer to the measurements made when the blood pressure was normal after operation. The solid and stippled bars indicate the averages of all the patients.

a room temperature of 27° C. with a humidity of 45 to 50 per cent. The peripheral blood flow and temperatures and other data recorded in Table I represent the averages of all the observations made for that morning.

Average preoperative*	69	37.54	33.86	35.0	35.0	35.0	34.6	34.2	33.6	34.6	33.0	32.7	32.5	32.0	178/120	76	+ 3	
Average postoperative†	50	37.01	33.49	34.6	34.6	34.3	33.8	33.2	32.6	33.9	32.8	32.6	33.0	34.2	124/ 89	78	- 7	
Standard deviations about the means preoperative	39	0.37	0.62	0.4	0.5	0.4	0.5	0.6	0.6	0.7	1.0	0.5	0.3	0.3	16/ 10	7		
Standard deviations about the means postoperative	10	0.11	0.35	0.4	0.6	0.2	0.4	0.6	0.6	1.0	0.7	0.5	0.3	0.3	11/ 8	9		

Smithwick Operation Followed by Moderate Decrease in Blood Pressure

R. L.	2/10/44*	81	33.97	34.7	34.7	34.4	34.6	33.9	33.6	35.1	33.9	33.3	32.5	33.4	212/136	92	- 5	Hypertension.
376201	2/21/44	99	34.24	34.1	34.9	34.6	35.2	34.2	33.7	34.8	34.4	33.0	33.3	34.5	168/123	93	+ 1	Chronic Glomerulonephritis.
M. 19	2/25/44	115	34.44	35.1	35.3	34.8	35.3	34.2	34.0	35.3	34.0	33.4	33.2	33.9	210/144	99	-10	Enlarged heart
	3/11/44	68	34.16	34.7	35.1	34.9	34.9	33.9	33.9	35.3	33.7	33.1	32.8	33.6	203/147	94	-10	
	3/14/44	70	34.20	34.1	34.7	34.7	35.3	34.0	34.2	35.3	34.1	33.2	32.9	33.8	216/145	88	-15	
	3/25/44	59	33.94	34.4	34.7	34.4	34.9	33.3	33.3	34.4	33.8	32.8	32.9	34.4	193/132	86	-15	
	5/31/44†	72	34.03	34.6	34.5	34.2	34.4	33.6	33.6	35.1	33.7	33.2	33.4	34.6	192/127	81	- 5	Postop. 3 mo
S. McD.	12/ 3/43*	25	33.52	34.9	34.5	33.7	33.5	33.9	33.6	34.2	33.1	32.2	33.0	32.5	177/113	68	-11	Hypertension. Enlarged heart
95209	12/21/43	47	33.53	35.2	34.2	33.8	34.1	34.0	33.9	34.6	32.5	32.1	32.2	33.3	156/110	90	- 3	
M. 48	1/ 4/44	55	33.72	35.1	34.6	34.0	34.3	34.0	34.3	34.8	33.2	33.3	31.8	32.5	162/108	74	- 6	
	3/29/44†	64	33.85	34.7	34.3	33.4	33.4	34.0	34.5	34.9	32.9	33.7	33.4	34.3	157/107	73	- 8	
W. C.	1/ 5/44*	62	34.30	35.3	35.1	34.5	34.7	33.7	34.2	35.0	33.7	33.5	33.2	34.4	198/113	66	- 1	Hypertension.
375325	1/ 7/44	70	33.97	35.0	34.8	34.3	34.3	33.8	34.2	34.8	32.9	33.2	32.9	34.5	193/112	66	- 2	Slight enlargement of heart.
M. 48	2/ 2/44	39	33.19	35.1	34.8	34.3	34.2	33.7	32.4	32.7	33.1	32.2	31.7	30.2	227/120	80	+ 7	
	2/ 3/44	32	33.73	34.9	34.9	34.6	34.7	33.7	33.4	34.1	33.2	33.3	32.1	32.1	216/123	80	+ 4	Myocardial infarction due to arteriosclerotic coronary thrombosis
	2/19/44	59	33.76	34.2	34.2	34.3	34.5	34.5	33.0	33.7	33.0	32.8	33.2	34.9	188/104	90	+ 4	
	2/26/44†	44	34.16	34.5	34.8	34.7	34.7	33.7	33.5	34.6	33.2	33.7	32.9	35.3	180/105	85	- 3	
M. J.	1/ 3/44*	82	34.51	35.1	35.1	35.1	35.2	34.6	34.2	35.2	34.1	33.7	33.6	33.7	241/126	65	- 2	Hypertension. Hypertensive encephalopathy. Enlarged heart
315435	3/ 7/44†	80	33.95	34.6	33.9	34.6	34.5	33.8	33.4	34.7	33.3	32.9	33.6	34.6	191/113	86	- 1	
F. 43																		
A. A.	2/27/42*	39	33.54	34.4	34.8	34.5	34.7	32.8	33.7	34.8	33.5	32.1	31.6	32.0	208/116	73	-10	Hypertension. Bronchial asthma.
318945	3/12/42	32	33.18	34.8	34.8	34.2	33.7	32.4	33.7	34.9	32.5	31.2	31.8	33.0	211/119	75	-10	Enlarged heart
F. 41	4/ 3/42†	12	33.37	34.3	34.2	34.7	33.8	32.7	33.0	34.8	32.4	31.2	32.5	34.0	181/116	75	-21	
I. H.	4/11/44*	33	32.01	32.2	32.7	32.3	32.4	32.4	32.4	32.9	31.6	31.2	31.2	31.2	221/148	85	+30	Hypertension
287756	5/10/44†	77	33.88	34.8	34.3	34.6	34.1	34.4	33.6	34.9	32.1	32.9	33.7	34.8	182/118	68	+10	

*Preoperative measurements which were used to obtain these averages or means.

†Postoperative measurements which were used to obtain these averages or means corresponding to the lowest blood pressure after operation.

‡R/L 40/21 = 40 days after operation on right side and 21 days after operation on left side.

TABLE I. OBSERVATIONS RELATING TO THE PERIPHERAL BLOOD FLOW, AND SKIN AND RECTAL TEMPERATURES IN HYPERTENSIVE PATIENTS BEFORE AND AFTER SPALPINECTOMY UNDERTAKEN TO LOWER THE BLOOD PRESSURE

NAME HIST. NO. SEX AGE (YRS.)	DATE	PERIPH- ERAL BLOOD FLOW C.C./M ² / MIN.	RECTAL TEMPER- ATURE ° C.	AVERAGE WEIGHT- ED SKIN- TEMPER- ATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS	TIME RELATION TO OPERATION
					° C.															
					1	2	3	4	5	6	7	8	9	10	11					
					° C.															
Smithwick Operation Followed by Decrease in Blood Pressure to Normal																				
E. C. 380212 F. 46	3/24/44* 4/17/44 5/ 5/44 6/ 9/44†	118 26 39 31	37.34 37.27 36.89 37.11	34.17 33.35 33.41 33.44	34.6 34.6 34.2 34.3	35.5 35.0 34.3 34.4	34.4 33.9 33.9 34.3	34.8 34.0 33.9 34.0	34.2 33.4 33.0 33.1	33.7 33.3 32.8 31.9	34.9 34.5 34.5 31.7	33.7 32.3 32.2 33.2	33.2 32.0 31.7 32.3	32.8 31.4 33.3 33.2	34.4 33.5 34.3 34.3	182/116 192/109 178/110 137/ 96	72 66 65 68	+12 - 3 - 5 - 4	Essential hyperten- sion. Enlarged heart	Preop. 13 d. after R. R/L 40/24† Postop. 2 mo.
L. H. 351566 F. 44	2/ 1/44* 2/12/44 2/14/44 3/ 4/44 3/10/44 6/10/44†	64 95 63 27 42 41	37.25 37.54 37.38 37.17 36.73 36.76	33.87 34.20 33.90 33.57 33.17 33.39	35.3 34.8 34.9 35.0 34.4 34.0	34.5 35.1 35.1 34.4 34.1 33.7	34.4 34.5 34.2 34.3 34.1 34.1	34.8 34.5 35.1 33.6 32.5 33.3	34.8 34.5 35.1 33.6 32.5 33.3	33.8 33.9 33.3 32.8 32.3 31.6	35.2 35.8 35.3 35.3 34.1 34.4	32.2 32.8 32.3 32.6 31.6 32.8	32.8 32.0 32.2 32.6 32.8 32.7	32.3 33.4 32.8 32.4 33.6 32.7	34.3 35.6 35.1 34.6 34.6 34.3	166/111 166/110 164/110 113/ 74 111/ 78 106/ 71	74 81 85 80 86 73	+ 2 + 8 0 -20 - 7 -10	Hypertension. En- larged heart	Preop. 10 d. after L. 12 d. after L. L/R 31/18 L/R 37/24 Postop. 4 mo.
C. D. 372511 F. 25	12/ 7/43* 1/18/44 1/21/44 2/ 4/44 2/23/44† 5/19/44	42 103 95 104 54 37	38.20 37.24 37.26 37.16 36.93 36.55	34.25 34.70 34.75 34.96 34.27 33.50	35.1 35.0 35.2 35.7 34.6 34.2	35.9 35.8 35.8 35.3 35.5 35.3	35.5 35.5 35.6 35.5 34.6 34.5	35.2 33.9 35.4 34.6 33.8 33.2	34.5 33.9 34.4 34.6 34.3 33.2	33.2 33.7 34.3 34.5 33.0 31.4	34.9 35.2 35.4 35.4 34.2 28.7	33.6 33.7 33.2 34.3 33.8 33.6	32.8 34.4 34.0 34.3 33.7 32.9	33.2 34.2 34.6 34.6 33.5 33.0	32.1 32.1 32.1 32.1 34.6 34.7	184/137 140/107 154/116 138/103 136/ 98 162/116	70 78 88 85 71 66	- 6 - 8 -16 - 9 -24 -14	Hypertension. Rheu- matic heart dis- ease. Mitral in- sufficiency and stenosis. En- larged heart	Preop. L/R 30/27 L/R 42/30 L/R 56/44 L/R 2 mo. 13 d./2 mo. 1 d. Postop. 5 mo.
O. K. 368408 F. 38	1/12/44* 1/25/44 2/ 8/44 2/11/44 2/28/44† 6/29/44	60 78 36 52 55 65	37.92 37.40 37.84 37.73 37.08 36.89	33.85 34.13 33.59 33.88 33.84 33.68	35.0 35.4 35.1 35.0 35.3 34.2	34.6 35.1 34.4 34.6 34.7 34.2	35.0 34.8 35.1 35.2 34.4 34.6	34.4 34.9 34.3 34.0 34.7 34.0	34.1 34.9 34.3 34.3 34.8 33.9	33.2 33.7 32.6 32.8 33.2 32.4	34.1 35.3 34.7 34.7 34.8 32.0	33.2 32.6 31.8 31.4 32.8 32.7	32.8 33.3 31.4 31.9 31.4 32.6	33.2 32.8 32.4 33.1 33.0 32.7	31.7 34.0 151/105 148/109 125/ 95 135/ 90	78 78 112 108 88 70	- 5 - 1 0 + 2 -11 - 9	Essential hyperten- sion	Preop. 12 d. after R. R/L 26/11 R/L 20/14 R/L 46/31 Postop. 5 mo.	
C. C. 311597 F. 44	1/ 5/42* 1/21/42 2/14/42†	32 55 65	37.08 37.42 37.07	33.26 33.22 33.56	34.5 35.1 34.8	34.5 35.3 34.6	35.6 34.9 34.2	34.1 34.9 34.2	33.1 33.8 32.7	33.4 33.9 32.9	34.4 34.8 33.7	32.7 32.9 32.2	32.4 32.9 32.9	32.4 32.0 33.0	27.6 30.7 33.0	169/117 175/125 132/103	79 87 96	- 4 +10 - 1	Essential hyperten- sion	Preop. 14 d. after R. R/L 22/17
B. G. 311888 F. 25	11/10/41* 1/14/42 4/ 9/42†	33 73 50	37.64 37.19 37.11	32.71 33.63 33.25	35.0 34.9 34.8	34.9 34.5 34.1	34.8 34.4 34.5	34.2 34.3 33.9	33.6 32.8 32.1	32.8 32.9 32.4	33.3 34.2 33.6	31.3 32.7 31.4	30.5 32.9 32.5	30.0 32.8 32.5	29.4 33.6 33.6	177/116 156/109 126/ 88	92 90 78	+14 + 5 - 2	Essential hyperten- sion. Enlarged heart	Preop. 27 d. after R. R/L 5 mo./ 4 mo.
G. L. 351331 M. 31 32	3/16/43* 3/22/43 4/15/43 6/20/44†	136 108 42 52	37.36 37.13 37.41 36.99	34.89 34.51 33.96 33.71	35.6 35.4 35.3 34.7	35.3 35.0 35.1 35.0	35.0 34.7 35.1 33.9	35.1 35.0 35.0 33.7	34.9 34.5 34.2 33.9	34.8 34.4 33.7 33.3	35.3 35.1 34.1 34.7	34.6 34.0 34.1 32.9	34.7 34.4 32.6 32.5	33.7 33.2 32.3 32.8	34.4 34.4 31.5 34.3	156/108 163/113 170/115 106/ 70	68 67 78 72	+ 6 + 3 +10 + 3	Essential hyperten- sion	Preop. 19 d. after L. L/R 15 mo./ 10 mo.

Average preoperative*		51	37.22	33.55	34.8	34.3	34.4	33.9	33.5	33.3	34.9	32.8	32.8	32.6	33.0	157/109	74	- 8
Average postoperative†		36	37.09	33.21	34.4	34.1	33.5	33.7	32.6	32.5	34.7	32.6	32.3	32.9	34.0	174/111	79	- 7
Standard deviations about the means preoperative		40	0.32	0.56	0.3	0.9	0.9	0.8	0.6	0.6	0.4	0.6	0.7	0.8	1.2	15/ 13	8	
Standard deviations about the means postoperative		21	0.12	0.31	0.9	0.5	0.3	0.7	0.8	0.6	2.9	0.5	0.9	0.4	0.3	14/ 10	13	
Partial Sympathectomy Followed by Moderate Decrease in Blood Pressure																		
E. L.	4/27/39*	50	37.24	32.70	33.8	34.0	33.5	33.3	32.0	32.7	33.4	32.0	31.4	31.3	32.4	220/130		-27
233250	5/ 6/39	37	37.12	32.61	33.4	34.2	33.8	33.3	32.5	32.8	33.2	31.0	30.9	31.4	32.4	214/112		+ 5
F. 43	5/18/39	10	37.32	32.07	33.3	34.4	32.9	33.9	31.8	31.7	33.2	31.1	30.7	30.4	30.6			+17
	6/ 6/39†	29	36.97	33.32	34.0	34.4	34.3	34.1	32.5	33.3	33.9	32.6	32.0	32.4	32.9	196/105		- 4
M. N.	4/28/39*	52	37.39	33.53	34.3	34.4	34.4	34.5	33.7	33.8	34.2	33.5	32.7	31.2	32.5	230/130		+16
231336	5/12/39	49	37.23	32.57	33.9	33.5	34.4	34.1	32.6	32.3	31.9	32.6	33.0	30.5	27.9	229/135		+ 9
F. 33	6/ 1/39†	42	36.95	33.61	34.4	34.0	34.5	34.3	33.0	33.8	34.7	32.7	33.3	32.1	33.7	200/132		- 1
A. R.	4/23/40*	73	37.11	33.49	35.1	34.6	34.6	34.5	34.5	34.1	34.4	33.3	33.4	31.9	29.6	187/124	69	-11
249201	5/ 1/40	74	36.92	33.77	34.7	34.3	33.6	34.0	33.9	33.7	34.5	33.3	33.9	33.1	33.4	127/ 96	68	-11
M. 40	5/10/40	11	37.37	32.46	34.9	35.2	33.5	33.5	33.2	33.5	34.1	31.6	31.3	29.9	26.4	158/117	78	- 7
	5/27/40†	21	37.12	33.06	34.5	33.9	33.8	33.6	33.8	33.9	34.2	33.0	33.4	32.1	27.2	149/104	70	-15
43	4/28/43	17	37.33	33.51	34.8	34.6	33.7	33.7	34.1	34.0	34.7	33.5	33.8	32.7	29.1	193/129	64	- 4
W. M.	2/ 6/39*	94	37.28	34.68	35.7	35.3	35.4	35.7	34.9	35.1	35.1	34.3	34.6	33.5	31.8	201/139		+22
224740	2/ 8/39	134	37.25	34.66	35.6	35.2	35.3	35.5	35.0	35.0	35.3	34.5	34.5	33.3	32.5	196/135		+10
M. 26	2/27/39	63	37.07	33.69	34.6	34.8	34.7	34.1	33.9	33.9	34.2	33.5	33.8	31.9	31.2	228/153		+ 5
	3/28/39†	68	37.09	34.32	35.3	35.3	34.6	35.1	34.5	34.4	34.7	33.2	33.8	33.7	32.4	177/136		-10
T. W.	2/29/40*	198	37.64	35.34	35.6	36.3	36.5	36.5	35.8	35.1	35.6	35.5	33.7	34.0	33.5	227/129	71	+22
243332	3/12/40	140	37.55	34.96	35.8	36.1	36.0	36.2	35.6	34.9	35.2	35.3	33.4	33.3	33.1	202/124	74	+13
F. 39	3/29/40	113	37.56	34.69	35.4	35.6	35.7	35.8	34.9	34.5	35.1	35.0	32.5	33.0	34.0	213/119	68	+ 8
	5/ 3/43†	132	37.35	34.40	35.2	35.5	35.5	35.5	34.1	34.3	34.7	34.0	33.0	33.0	33.4	193/127	66	+19
Average preoperative*		97	37.33	33.95	34.9	34.9	34.9	34.9	34.2	34.2	34.4	33.7	33.2	32.4	32.0	213/130		+ 4
Average postoperative†		78	37.10	33.74	34.7	34.6	34.5	34.5	33.6	34.1	34.4	33.1	33.1	32.7	31.9	183/121		0
Standard deviations about the means preoperative		55	0.18	0.94	0.7	0.9	1.0	1.1	1.3	0.9	0.8	1.2	1.1	1.2	1.3	16/ 6		
Standard deviations about the means postoperative		44	0.56	0.50	0.6	0.7	0.6	0.7	0.7	0.4	0.3	0.5	0.6	0.6	2.4	19/ 14		

TABLE I—CONT'D

NAME INST. NO. SEX AGE (YRS.)	DATE	PERIPH- ERAL BLOOD FLOW C.C./M ² / MIN.	RECTAL TEMPER- ATURE ° C.	AVERAGE WEIGHT- ED SKIN TEMPER- ATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS	TIME RELATION TO OPERATION
					1	2	3	4	5	6	7	8	9	10	11					
					° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.	° C.					
Smithwick Operation Followed by Moderate Decrease in Blood Pressure—Cont'd																				
V. K.	4/ 5/44*	25	36.94	32.25	34.4	34.3	32.8	32.2	33.4	32.3	32.7	32.0	30.1	30.2	31.5	234/121	91	+33	Hypertension. En- larged heart. Arteriosclerotic heart disease	Preop. L/R 24/13
308001	5/11/44†	94	37.61	33.98	35.3	35.8	34.5	34.3	33.9	33.8	34.2	33.1	31.9	32.3	35.1	190/100	104	+35		
M. 51																				
Average preopera- tive*		50	37.21	33.44	34.4	34.5	33.9	33.9	33.6	33.4	34.3	33.1	32.3	32.3	32.7	213/125	76	+ 5		
Average postopera- tive†		63	37.18	33.89	34.8	34.5	34.4	34.2	33.7	33.6	34.7	33.0	32.8	33.1	34.7	182/112	82	+ 1		
Standard deviations about the means preoperative		23	0.26	0.90	0.9	0.8	0.8	1.0	0.7	0.7	1.0	0.9	0.9	1.1	1.1	20/ 12	9			
Standard deviations about the means postoperative		25	0.23	0.40	0.3	0.6	0.4	0.5	0.6	0.4	0.3	0.5	0.9	0.5	0.4	12/ 12	10			
Smithwick Operation Followed by No Change in Blood Pressure																				
P. L.	3/ 1/42*	16	37.20	33.07	34.6	34.0	33.5	34.0	32.6	32.7	34.8	32.5	31.9	32.4	30.8	168/121	67	-22	Hypertension	Preop. 11 d. after L. L/R 32/17 Postop. 1 yr.
319076	3/30/42	22	37.11	32.97	34.2	34.1	33.3	33.0	32.1	32.2	34.4	32.4	31.3	32.0	34.3	170/119	65	-24		
M. 24	4/20/42	8	37.07	32.41	33.9	33.2	32.6	32.5	31.2	31.6	33.8	31.8	31.1	32.2	33.3	181/125	75	-24		
25	5/ 4/43†	13	37.06	32.80	35.3	34.3	33.1	33.0	31.3	31.3	28.5	33.0	31.0	33.3	34.0	186/128	64	-16		
C. N.	5/31/44*	71	37.38	33.92	35.1	35.0	34.9	34.4	34.1	33.7	35.4	33.1	33.4	31.9	32.9	140/ 85	66	+ 1	Essential hyperten- sion. Enlarged heart	Preop. 12 d. after L. L/R 25/12
386902	6/14/44	78	37.20	33.77	35.0	34.4	34.5	34.2	33.7	32.9	34.1	33.1	32.3	33.3	34.0	181/101	68	+ 5		
F. 42	6/27/44†	73	37.06	33.72	34.6	34.7	34.1	34.4	32.9	32.9	34.0	33.2	32.9	33.0	34.3	183/ 96	64	+ 1		
S. C.	5/27/44*	32	37.22	33.11	34.3	33.7	33.6	33.1	33.5	32.7	34.4	32.4	32.2	32.1	33.2	150/107	73	- 4		
384676	6/13/44	47	37.57	33.29	33.1	33.8	34.4	33.4	33.5	33.2	34.5	32.2	33.1	33.0	34.1	183/128	106	+10	Essential hyperten- sion. Enlarged heart	Preop. 12 d. after L. L/R 27/12
F. 33	6/28/44†	41	37.20	33.31	33.9	33.5	33.4	33.2	33.6	32.8	33.3	32.4	33.1	33.2	34.3	161/108	94	0		
I. R. S.	4/ 4/44*	16	37.23	33.17	34.7	34.1	32.9	32.8	32.9	33.0	34.6	32.0	32.8	32.8	33.5	182/118	71	- 4		
381016	5/18/44†	27	37.23	33.02	34.8	34.5	33.6	32.6	32.5	32.5	34.3	31.9	31.5	32.1	33.8	188/111	94	- 8		
F. 50																			Hypertension	Preop. 14 d. after R. R/L 30/13 Postop. 3 mo.
T. G.	1/ 5/42*	119	37.07	34.47	35.2	34.9	34.9	35.0	34.1	34.3	35.2	33.8	33.7	33.9	34.4	146/116	92	- 9		
311596	2/ 4/42	160	37.24	34.79	35.2	35.5	35.1	35.6	34.5	34.4	35.3	34.2	34.1	34.0	34.9	220/166	103	- 5		
M. 13	2/20/42	87	37.32	34.26	35.2	34.9	34.8	35.1	33.7	33.6	34.3	33.4	33.0	33.9	34.5	176/142	110	- 7		
	5/ 7/42†	28	36.89	33.22	33.4	33.5	33.5	33.5	32.9	33.1	33.3	32.6	32.9	33.1	33.6	153/114	78	-10		

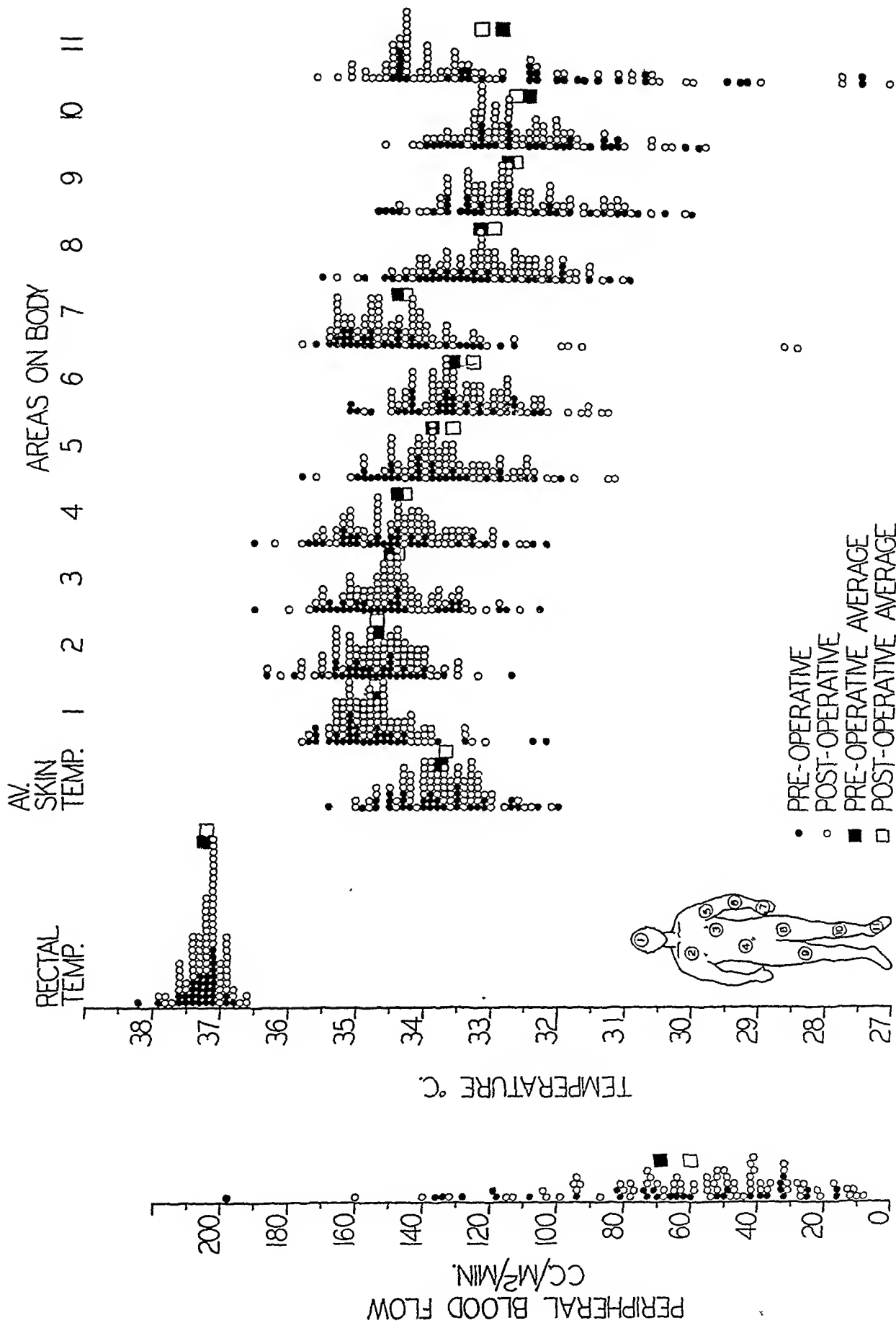


Fig. 2.—In this figure are shown all the preoperative (open circles) and all the postoperative measurements (closed circles) on all patients (Table I). The corresponding averages of all patients are shown in open and solid squares, respectively (for description, see text). If this chart is examined with the peripheral blood flow heading down, it is a series of frequency curves.

TABLE I—CONT'D

NAME LIST. NO. SEX AGE (YRS.)	DATE	PERIPH- ERAL BLOOD FLOW C.C./M ² / MIN.	RECTAL TEMPER- ATURE ° C.	AVERAGE WEIGHTED SKIN TEMPER- ATURE ° C.	TEMPERATURE OF ELEVEN AREAS ON BODY SURFACE											BLOOD PRES- SURE MM. HG	PULSE RATE PER MIN.	BASAL META- BOLIC RATE PER CENT	DIAGNOSIS	TIME RELATION TO OPERATION
					° C.															
					1	2	3	4	5	6	7	8	9	10	11					
Partial Sympathectomy Followed by No Change in Blood Pressure																				
M. H.	11/10/39*	66	37.08	33.73	34.8	34.5	35.2	35.2	33.6	33.4	33.5	33.4	31.6	31.4	27.6	219/129	96	+ 8	Hypertension.	Preop.
250110	11/30/39	49	37.48	33.04	34.7	34.1	34.7	34.9	33.5	33.6	33.6	32.7	30.2	30.7	31.0	217/121	93	+ 9	Slight cardiac enlargement	16 d. after R. E/L 35/11
R. 33	12/19/39†	42	37.77	33.25	34.6	34.0	34.5	34.2	33.3	33.2	33.9	32.5	31.7	31.1	33.2	213/128	100	+15		
A. B.	2/14/40*	128	37.24	34.25	35.1	35.3	35.4	35.6	34.7	34.2	34.0	34.9	33.4	33.8	30.8	173/124	68	- 4	Malignant hypertension	Preop.
256256	3/ 1/40	81	37.19	33.96	35.2	35.4	35.1	35.1	34.3	33.9	33.7	34.2	32.6	32.5	30.7	179/135	93	-13	sion. Enlarged heart. Mitral insufficiency. Mitral stenosis.	3 d. after L. L/R 27/13
M. 19	3/19/40†	48	36.93	34.01	34.9	34.8	35.1	35.2	34.0	33.8	34.0	34.1	33.0	33.2	31.0	171/121	65	- 3		Postop. 15 mo.
20	6/17/41	46	36.63	33.33	34.0	34.4	34.4	34.4	33.2	32.8	33.1	33.3	32.2	32.6	30.7	181/126	63	- 6		Preop.
21	3/25/42*	49	37.12	33.81	34.5	35.0	35.2	35.1	34.1	33.6	33.7	33.9	33.1	32.8	29.3	196/127	59	- 0	Encephalopathy	11 d. after R. E/L 32/14
	4/15/42	52	37.11	33.77	34.6	34.8	35.0	34.7	34.1	33.5	34.2	34.0	33.4	32.3	30.1	175/121	80	- 5		Preop.
	5/ 6/42†	53	36.96	33.27	33.4	34.0	33.8	33.8	33.1	33.1	34.0	33.3	32.5	32.7	32.0	180/132	72	- 2		Postop. 1 yr.
22	6/11/43	94	37.55	34.39	34.9	36.3	35.0	35.1	34.2	34.2	35.0	34.5	33.2	32.9	34.3	203/139	70	+ 5		Preop.
23	6/16/44	88	36.99	34.24	34.6	35.2	34.3	35.2	33.9	33.6	34.8	34.0	32.9	33.2	34.9	205/141	73	+11		
Average preoperative		81	37.15	33.93	34.8	34.9	35.3	35.3	34.1	33.7	33.7	34.1	32.7	33.0	29.2	196/127	74	- 1		
Average postoperative		48	37.22	33.51	34.3	34.3	34.1	34.4	33.5	33.4	34.0	33.3	32.7	32.3	32.1	188/127	79	0		
Standard deviations about the means preoperative		22	0.07	0.25	0.3	0.4	0.1	0.2	0.5	0.4	0.2	0.6	0.8	1.0	1.3	18/ 2	17			
Standard deviations about the means postoperative		5	0.39	0.35	0.7	0.4	0.6	0.6	0.4	0.3	0.1	0.7	0.6	0.9	0.9	18/ 5	15			
Average of all preoperative measurements		69	37.25	33.75	34.7	34.7	34.5	34.4	33.9	33.6	34.4	33.2	32.8	32.5	32.9	189/120	73	- 3		
Standard deviations about the means		41	0.27	0.77	0.6	0.7	0.9	1.0	0.8	0.8	0.8	1.0	1.2	1.0	2.0	28/ 13	9			
Average of all postoperative measurements		60	37.20	33.68	34.7	34.7	34.4	34.3	33.6	33.3	34.3	33.0	32.7	32.7	33.2	175/116	79	- 3		
Standard deviations about the means		32	0.86	0.55	0.5	0.6	0.6	0.8	0.8	0.8	1.2	0.9	0.8	0.9	2.0	30/ 18	12			

In those patients subjected to the Smithwick procedure in whom the blood pressure fell to normal after operation, the temperature of the upper part of the body fell after operation and the temperature of the lower part rose as much as 2.2°C . in the feet; the peripheral blood flow decreased; the rectal temperature, which was elevated, decreased; and the average weighted skin temperature decreased. The weighted fall in the upper part more than balanced the rise in temperature of the lower extremities. These temperature changes are shown graphically in Fig. 1. Before operation (open circles) the symbols representing the rectal, average skin, and the temperatures of Areas 1 to 8 are mostly at the upper part of the chart, while those of Areas 10 and 11 are mostly at the lower part. After operation (closed circles), the rubrics representing the rectal, average skin, and the temperatures of Areas 1 to 8 move down, but those representing the temperatures of Areas 10 and 11 move up. Though this is the trend, only the change in the foot temperature is of statistical significance. Before operation, in the group in which the Smithwick operation produced a moderate fall in blood pressure, the rectal temperature was slightly elevated, the average weighted skin temperature was slightly decreased, but the temperatures of the areas of the skin were essentially normal except for the lower thigh and leg which were cooler; the peripheral blood flow was decreased. After operation, the average weighted skin temperature rose as did the temperature of most of the areas of the body, the greatest rise, 2°C ., being in the feet. The peripheral blood flow rose.

Those in whom there was no fall in blood pressure after operation had, before operation, essentially the same characteristics in their measurements as did the preceding group. After operation there was a fall in rectal temperature; the average weighted skin temperature fell, as did the temperatures of the individual areas for the upper part of the body, with the exception of the feet in which the temperature rose 1°C . only. The peripheral blood flow decreased as would be expected with the lower skin temperature.

In those patients subjected to partial sympathectomy the peripheral blood flow decreased and the weighted skin temperature fell. Those in whom the lowering in blood pressure was moderate showed very slight fall in foot temperature, and those in whom the blood pressure was unchanged showed a rise in foot temperature.

Out of these observations no patterns appear which relate the amount of peripheral blood flow to the level of blood pressure following sympathectomy. The average weighted skin temperature rose or fell according to whether the peripheral blood flow increased or decreased after operation. There was, on the whole, rise in the foot temperature as a result of operation, the most marked increase being in those who had the more extensive operation (Smithwick) and in whom there was fall in blood pressure.

Fall in blood pressure to normal after the Smithwick operation occurred in six women but in only one man. When this group of six women is analyzed for the changes occurring after operation, they show the same general trends as the group as a whole, namely fall in peripheral blood flow, fall in rectal temperature, fall in average weighted skin temperature, and fall in temperature of the upper part of the body and rise in temperature of the lower part of the

areas of the body except Area 2 (upper chest) rose, but the increases were not statistically significant. The greatest increase, a rise of 2° C., was in the feet (Area 11); this rise occurred consistently and was significant. The increase of 0.8° C. in the temperature of the leg (Area 10) was not significant. The peripheral blood flow rose from 50 c.c. to 63 c.c. per square meter per minute, which was statistically significant.

Observations Relating to Patients Subjected to the Smithwick Operation in Whom No Change in Blood Pressure Occurred.—Five patients, two men and three women, comprise this group (Table I, Fig. 2). The preoperative levels of blood pressure in this group was lower than in the other group, namely 157/109. After operation, the rectal temperature fell slightly, the average skin temperature fell, and the temperature of areas of the body from 1 to 9, inclusive, fell; these areas include the forehead (Area 1), the upper chest (Area 2), the lower chest (Area 3), the abdomen (Area 4), the upper arm (Area 5), the forearm (Area 6), the hand (Area 7), the upper thigh (Area 8), and the lower thigh (Area 9). The temperature of the leg (Area 10) increased only 0.3° C. and that of the foot (Area 11) only 1° C. as compared with a 2.2° C. rise in the group of patients whose blood pressure fell after operation. These changes are not significant. Decrease in peripheral blood flow from 51 c.c. to 36 c.c. per square meter per minute did not appear significant, though this group which includes only five patients is small for statistical analysis. In the five patients of this group the blood pressure rose after operation instead of falling; the average was 174/111 after operation as compared with 157/109 before operation.

Observations Relating to Patients Who Experienced Partial Sympathectomy in Whom Moderate Fall in Blood Pressure Occurred.—Five patients, two men and three women, comprise this group. The average blood pressure fell from 213/130 to 183/121 after operation. After operation (Table I, Fig. 2) no significant changes occurred in the rectal, average weighted skin, and local temperatures, or in peripheral blood flow. There was not the rise in temperature of the feet which was observed following the Smithwick procedure.

Observations Relating to Patients Having Partial Sympathectomy in Whom a Fall in Blood Pressure Did Not Occur.—This group comprises one man and one woman. A. B. was subjected to the more extensive procedure two years after the partial operation. After operation (Table I, Fig. 2) the only significant change was the rise of 2.9° C. in the temperature of the foot (Area 11).

DISCUSSION

Observations relating to peripheral blood flow have been made in patients before and after sympathectomy designed to lower the blood pressure. The Smithwick procedure was more effective for this purpose than was partial sympathectomy. The data have been analyzed so that the behavior of the peripheral blood flow could be related to the response to the operation.

In all the small groups of hypertensive subjects, the trend, before operation, was for the temperature of the upper part of the body to be warmer than normal, and for the temperature of the lower part of the body to be cooler than normal.²⁸

The data relating to the basal metabolic rates are of interest. Those patients in whom the blood pressure fell to normal (Smithwick) showed a fall in the basal metabolic rate from +3 per cent to -7 per cent, a fall of 10 per cent; those showing slight fall in blood pressure (Smithwick and partial sympathectomy) showed a fall in rate of 4 per cent; and those whose blood pressure was not altered (Smithwick and partial sympathectomy) showed no change in the basal metabolic rate.

In the group of hypertensive patients considered in this paper, there is a linear relationship between peripheral blood flow and average weighted skin temperature before operation (Fig. 3), just as there was in the larger group already reported.¹ This relationship is maintained after operation, but the correlation is even more striking and fewer points fall outside the zone showing the closest correlation (Fig. 4).

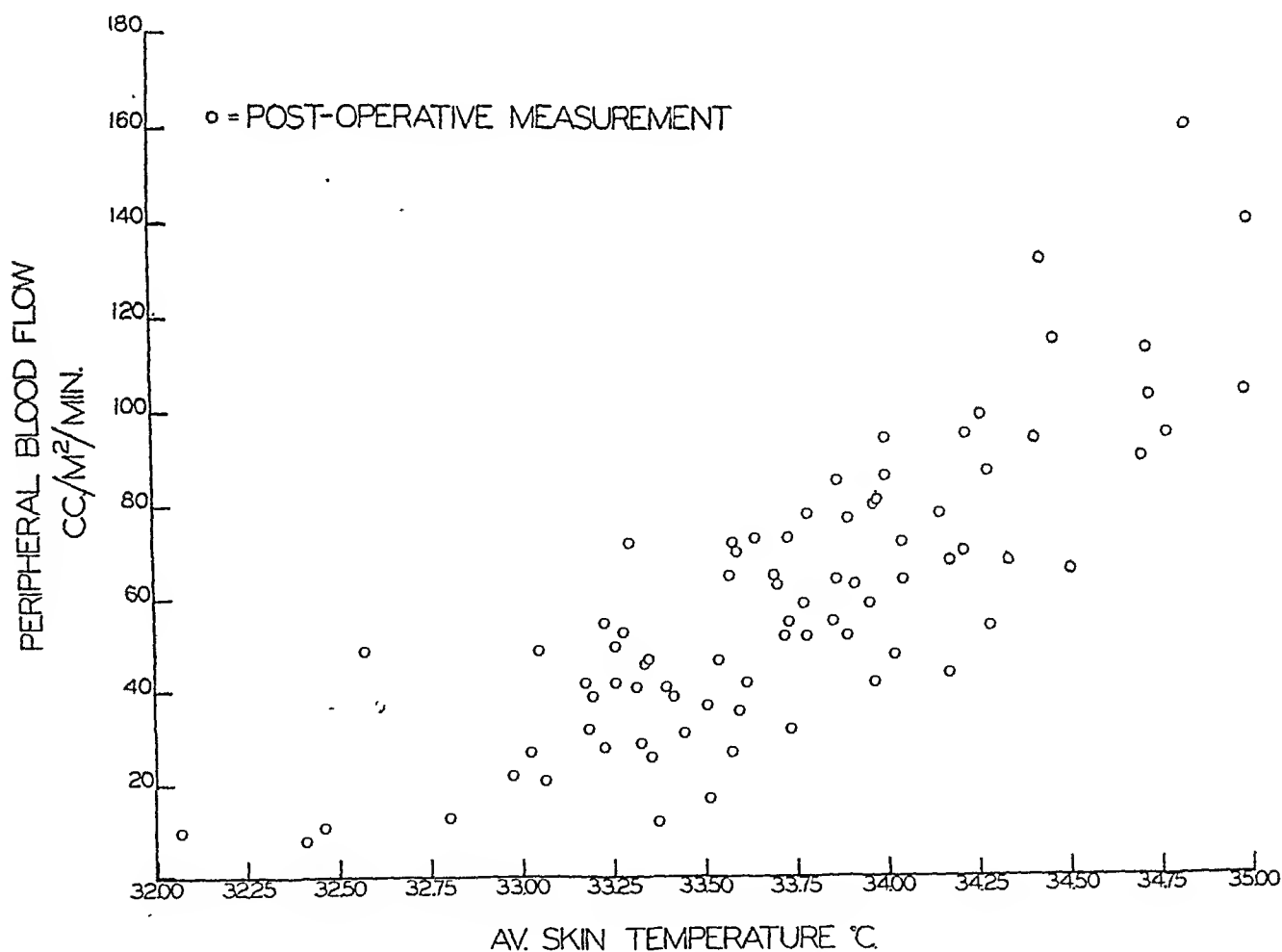


Fig. 4.—In this figure all the postoperative measurements of peripheral blood flows of all patients (Table I) are plotted against the corresponding average skin temperatures (Table I) revealing a very close correlation. Most of the points which were out of line with this correlation in Fig. 3 were in the preoperative measurements of the patients.

SUMMARY

The peripheral blood flow has been measured by a modification of the method of Hardy and Soderstrom in patients with arterial hypertension before and at intervals after splanchnic resection, undertaken with the intent of lowering the blood pressure. In addition observations were made of the skin and

body. From these observations we could not detect any characteristics which set those patients apart from those who failed to experience a fall in blood pressure.

In those patients subjected to the Smithwick procedure and to partial sympathectomy, all the measurements before operation were averaged and compared with the corresponding estimations after operation (Table I, Fig. 2). Likewise all the preoperative as well as the postoperative measurements of all patients subjected to any form of sympathectomy were averaged. The changes for the entire group of patients are less marked, because the changes shown in those groups in which marked changes occurred are pulled out of line by those in which no changes occurred. The trends, as shown in the frequency diagram (Fig. 2) are, however, essentially the same as in the smaller groups, but are not of statistical significance.

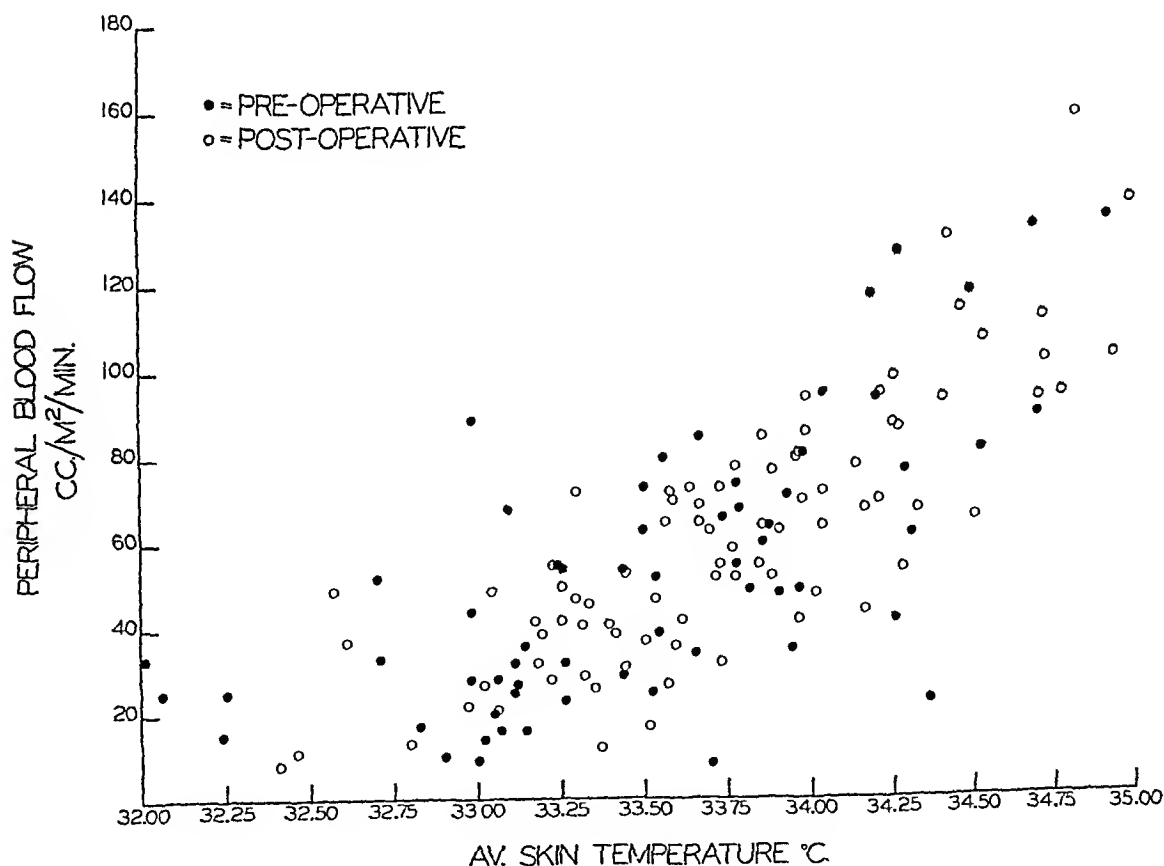


Fig. 3.—In this figure all the peripheral blood flows of all patients (Table I) are plotted against the corresponding average skin temperatures before (closed circles) and after (open circles) operation. A linear relationship is apparent in that the higher average skin temperatures were associated with the higher peripheral blood flows.

The colder feet and lower parts of the body in hypertension may be due to increased vasoconstriction in these regions and in the splanchnic area, which is relieved by splanchnic resection. The marked rise in foot temperature is what is to be expected from including the section of the second lumbar ganglion in the operative procedure.

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rectal temperatures. In 19 patients the Smithwick procedure was carried out, and in seven operated upon earlier, the less extensive operation was done. The following facts emerged:

1. In these patients the Smithwick procedure was more effective in lowering the blood pressure than the less extensive splachnic resection.

2. Since the objective of the operation is to lower the blood pressure, the groups in which this occurred are of special interest with respect to peripheral blood flow. The most marked differences in the observations made before and after operation were recorded in the group in which the blood pressure fell to normal after operation. The peripheral blood flow decreased, the rectal temperature fell, the average weighted skin temperature fell, the temperature of the upper part of the body fell; the temperature of the lower part of the body, especially of the feet, rose. The effects were less in those with less marked fall in blood pressure or without change in blood pressure.

3. There was, however, no pattern discernible in the individual peripheral blood flows when these were analyzed in relation to the effect of the surgical procedure either in those in which the blood pressure fell to normal or in those showing less benefit from the operation.

4. The peripheral blood flow in hypertension bears a linear relationship to the weighted skin temperature. This relationship is especially close after splenchnic resection.

5. In those patients exhibiting the most marked lowering of blood pressure after operation, the average skin temperature fell after operation. The temperature of the upper part of the body, which before operation was warmer than normal, fell; the temperature of the feet, which before operation was cooler than normal, rose after operation. The elevated rectal temperature in hypertension falls after operation.

6. In those patients showing a fall in blood pressure to normal after operation, the mean basal metabolic rate decreased 4 per cent, and in those whose blood pressure was not lowered, no change in the mean basal metabolic rate occurred.

7. While the peripheral blood flow is, on the average, lower in hypertensive than in normal subjects,¹ there are wide ranges, and the differences are not significant. The level of blood pressure has no relation to peripheral blood flow either where the blood pressure is high or in the same patient after restoration of normal blood pressure.

It is likely that the mechanism, whatever it may be, which is responsible for the elevation of blood pressure in hypertension is also responsible for the differences in local skin temperatures which hypertensive patients exhibit when compared with normal individuals.

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average onset occurred at about the seventieth day. They varied in intensity from slight visual blurring, slight tingling of the extremities, or slight muscular weakness to extensive generalized paralysis with muscular wasting. Recovery was usually slow, averaging about one hundred days, but the ultimate prognosis was excellent.

A severe myocarditis, with rapidly fatal outcome, occurred as a complication in one of the first patients admitted in the epidemic. During the same week a similar fatality occurred in a near-by hospital. As a result, tremendous respect was engendered for this potentially lethal complication of what was otherwise an essentially benign, although prolonged and incapacitating disease. Consequently, in all patients in whom the diagnosis of cutaneous diphtheria was suspected, every effort was made to prevent the development of a cardiac complication or, if this was impossible, to detect and treat it at the earliest possible stage of development. With these objectives in view, all patients in whom the diagnosis of cutaneous diphtheria was suspected were isolated at complete bed rest as patients of the dermatology section, where local therapy was given. The policy with respect to the administration of antitoxin was at first poorly defined, but as soon as we became certain that we were dealing with cutaneous diphtheria in epidemic proportions, a definite policy for the administration of antitoxic serum was established: 20,000 to 40,000 units of diphtheria antitoxin were promptly administered to all patients in whom active cutaneous diphtheria was diagnosed clinically. Contrary to other reports, we are convinced that this disease can be accurately diagnosed by an experienced dermatologist, particularly in the height of an epidemic. As soon after admission as feasible, the patients were examined for any evidence of cardiac disease, and an electrocardiogram was taken. Thereafter, tracings were repeated every ten to twenty days until the lesions had become definitely inactive. Any patient who exhibited symptoms, signs, or electrocardiographic changes suggestive of cardiac involvement was observed especially closely and was studied frequently with the electrocardiograph. When cardiac involvement was definitely diagnosed or considered probable, the patient was continued at bed rest until all evidence of the cardiac complication had disappeared.

Myocarditis: Incidence, Time of Onset, Duration.—In the 140 patients with cutaneous diphtheria, myocardial complication was diagnosed as a certainty in four, one of whom died, and was considered probable in three others. The incidence was 5 per cent. In several additional patients it was considered possible that a minimal myocarditis had occurred, but the diagnosis could not be definitely established.

The earliest appearance of an electrocardiographic abnormality was on the twentieth day after the onset of the cutaneous lesions. In the patient who died on the forty-first day of his cutaneous disease, symptoms of cardiac disease first appeared about the thirty-eighth day. In another patient, the myocarditis was first diagnosed as late as the sixtieth day, although it may have been present for some time before this, inasmuch as the patient was not admitted to the hospital until the fiftieth day, had no cardiac symptoms, and did not have an

MYOCARDIAL COMPLICATIONS OF CUTANEOUS DIPHTHERIA

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THE diagnosis of cutaneous diphtheria was made in 140 American soldiers admitted to a United States Army General Hospital in the India-Burma Theater during the period from July through December, 1944. The myocardial complications observed in these patients are considered in this report. Data are presented with reference to the incidence, predisposing factors, time of onset, duration, symptomatology and course, physical findings, electrocardiographic studies, associated neuritic complications, treatment, and ultimate disposition of these patients. None of the patients of the cutaneous diphtheria series who developed a cardiac complication had had clinical evidence of faucial diphtheria.

A communication dealing especially with the dermatological aspects of cutaneous diphtheria, including data with reference to the epidemiology, incidence, predisposing factors, description of the lesions, laboratory findings, treatment, and ultimate results, is to be published.¹ A separate report of the neurological complications of the disease is also to be published.²

The cases of cutaneous diphtheria considered in this report occurred almost exclusively in combat soldiers who had been evacuated during or after a strenuous campaign fought in jungles, marshes, and foxholes during the wet monsoon in Burma. Wet feet, poor foot hygiene, multiple minor abrasions, and insect and leech bites were undoubtedly important predisposing factors to the development of the cutaneous lesions. These lesions, which are described in detail elsewhere,¹ were ulcerative, usually with a membrane or a leathery, black, adherent, inlaid crust. The lesions were usually multiple, and predominantly affected the extremities. They were extremely resistant to treatment, and in many instances persisted for many weeks or months.

Although diphtheria was early suspected as the cause of the skin lesions, conclusive laboratory proof was not obtained until several weeks later. Organisms having the morphologic appearance of Klebs-Löffler bacilli were recovered in approximately 80 per cent of the 109 patients in whom the skin infection was still active at the time of admission, but at first the fermentation reactions appeared to indicate that these organisms were not diphtheria bacilli. Later, however, a change was made in technique with the result that virulence-positive Klebs-Löffler bacilli were recovered in 26 of the last 38 cases.

Neurological complications, described elsewhere,² developed in 43.5 per cent of these patients. They first appeared as early as the twenty-third day of the skin lesions or as late as the one hundred fifty-eighth day; the

Laboratory findings were generally normal. A leucocytosis of 22,000, predominantly polymorphonuclear, was present on the day of death in the one patient. In the others the leucocyte count was normal; if any slight elevations were present they could be accounted for on some other basis. Sedimentation rates, taken on five of the seven patients, were normal.

Autopsy Findings.—At post-mortem examination of the one patient who died, the heart was flabby and slightly dilated. The pericardium contained 100 c.c. of straw-colored fluid. The epicardium, endocardium, and pericardium were speckled with many petechial hemorrhages. The myocardium was pale brown with grayish streaks. Microscopic examination revealed extensive fragmentation and disintegration of the muscle fibers, with degeneration, nuclear changes, and interstitial cellular infiltration, predominantly lymphocytic.

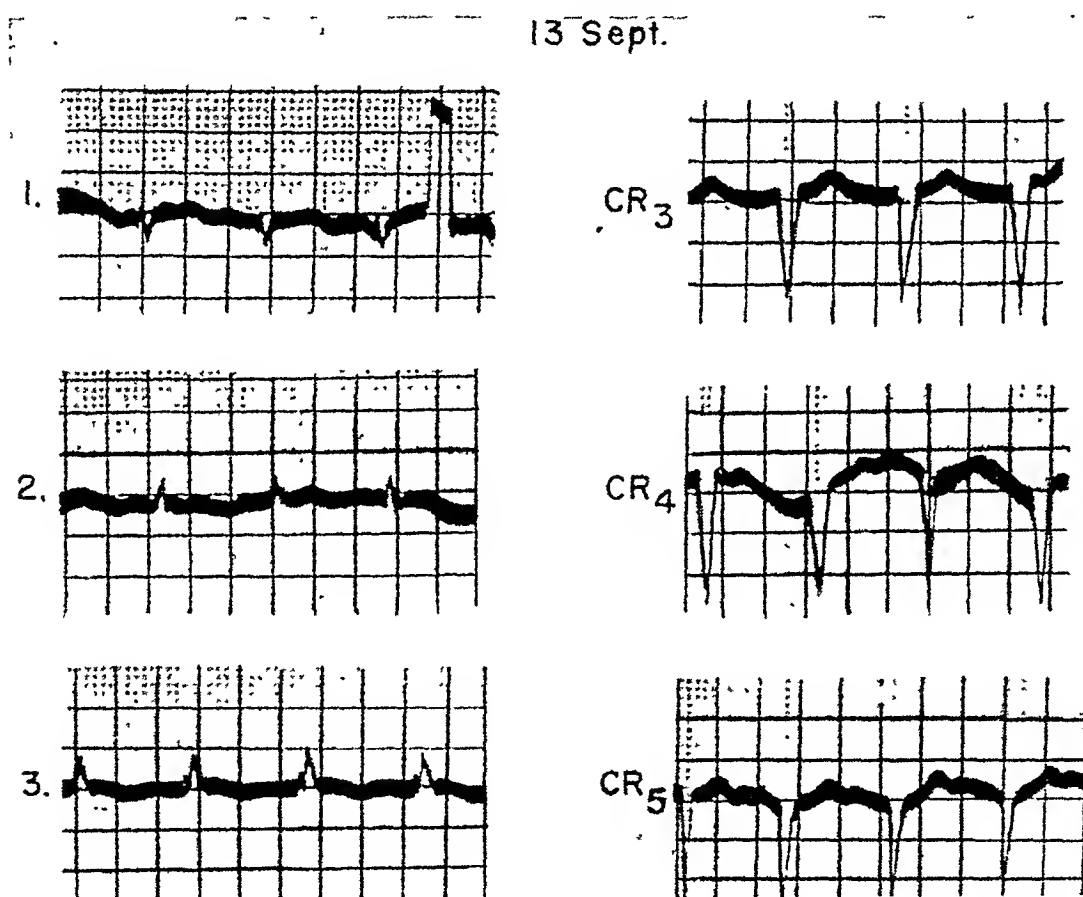


Fig. 1.—Definite myocarditis. Onset of cutaneous diphtheria August 3. Severity of lesion graded as 4 plus. There was no neuritis. Antitoxin was not given. The onset of cardiac symptoms was September 10. These consisted of abdominal pain, dizziness, dyspnea, vomiting, chest pain, and collapse. Death occurred on September 13. The electrocardiograph showed a rate of 110, with a regular rhythm. The P waves cannot be definitely identified. The QRS complexes in the limb leads were of low voltage and slurred. There were deep Q waves in all chest leads. The T waves are of low amplitude. The electrocardiographic diagnosis was "abnormal tracing, probably indicative of myocarditis."

Electrocardiographic Findings.—The electrocardiograph provided by far the most reliable and, in four instances, the only means of establishing the diagnosis of diphtheritic myocarditis. In all, 381 tracings were taken in the study of the 140 patients in whom the diagnosis of cutaneous diphtheria was made; in addition, tracings were taken on several patients with ulcerative skin lesions but in whom the diagnosis of diphtheria was ultimately excluded.

electrocardiogram taken until the sixtieth day. In general, the period of the fourth to the seventh week of the cutaneous diphtheria appeared to be that in which myocarditis developed, if at all.

The duration of the myocarditis ranged from twenty-eight to fifty days in those in whom the diagnosis was considered probable, and from sixty to ninety days in those in whom it was certain, excepting, of course, the one patient who died four days after the onset of symptoms. Cardiac abnormality did not persist beyond one hundred forty days from the onset of the cutaneous lesions in any patient.

Clinical Symptoms and Signs.—With few exceptions, symptoms were by far more frequent and more striking in those patients who did not have any evidence of organic cardiac disease than in those who had real cardiac complications. Typical cardiac neurosis phenomena, such as palpitation, tachycardia, stabbing precordial pains, and tachypnea, occurred with great frequency on the cutaneous diphtheria wards, especially after the death of the one patient. Of the seven patients in whom the diagnosis of myocarditis, definite or probable, was made, four had no symptoms which could be considered as cardiac in origin. Had these patients been allowed activity, it is quite possible that symptoms would have appeared. Of the other three, two complained of dyspnea and faintness upon slight exertion. The third patient, the one who died, first complained of aching right-sided abdominal pain with nausea and some breathlessness on exertion. These symptoms increased but were not incapacitating or severely distressing until eighteen hours before death when the discomfort extended upward into his chest as a steady dull pain; he began to vomit profusely, became very dizzy, and collapsed beside his bed. In spite of rest, morphine sedation, and oxygen, dyspnea and faintness persisted until death. It is interesting, and probably significant, that palpitation was never a symptom in any patient with myocarditis.

In the patient who died, whose symptoms have been described, the most striking physical sign was extreme pallor, despite a completely normal hemoglobin. The patient appeared moderately dyspneic; the neck veins were engorged, and the liver was enlarged and tender. There was no definite evidence of cardiac enlargement; precordial pulsation was not visible. Although the cardiac sounds were barely audible, there was a distinct gallop rhythm. The pulse was extremely feeble with a rate of 110. The systolic blood pressure was 60 mm. Hg; the diastolic pressure could not be determined.

In the other six patients, the physical signs were not striking. Tachycardia was absent; the heart rate at rest did not exceed 90 beats per minute. Two of the patients had occasional extrasystoles. The blood pressure was below 100, systolic, in only two instances; a pressure of 90/50 was the lowest reading obtained. The neck veins were not engorged. The heart was not enlarged on physical examination in any of these patients, although in one x-ray films showed slight but definite enlargement. Later the heart became normal in size. Precordial pulsations and cardiac sounds were definitely feeble in two of the patients; in the others they were normal. No murmurs or friction rubs were heard.

From an analysis of these tracings, several conclusions could be drawn: (1) Tachycardia was not an important feature. (2) Extrasystoles were observed no more frequently than one would expect in a group of normal individuals. (3) P-R interval prolongations above 0.20 second were not observed in any patient in

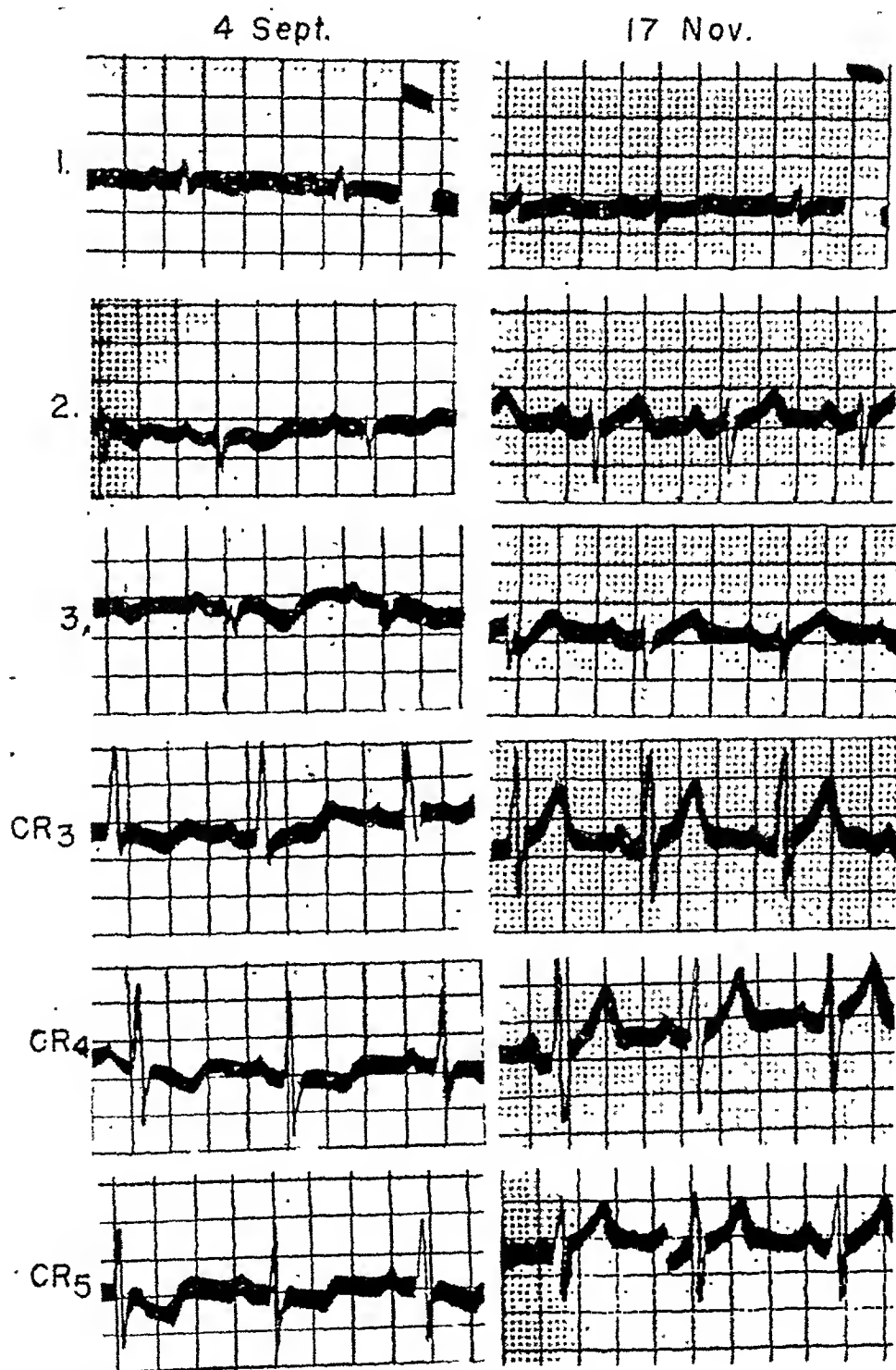


Fig. 3.—Definite myocarditis. Onset of cutaneous diphtheria July 1. Severity of lesions graded as 4 plus. Severe neuritis set in on the fifty-fourth day and lasted one hundred eighty-four days. No antitoxin was given. Cardiac symptoms appeared on the fifty-sixth day and consisted of dizziness and dyspnea. On September 4 the electrocardiograph showed a rate of 80, with a sinus rhythm. The P-R interval was 0.16 second. The QRS complexes were of very low amplitude. The T waves were inverted in all leads. The amplitude of the QRS complexes showed a progressive increase. On November 17 the T waves became upright in all leads.

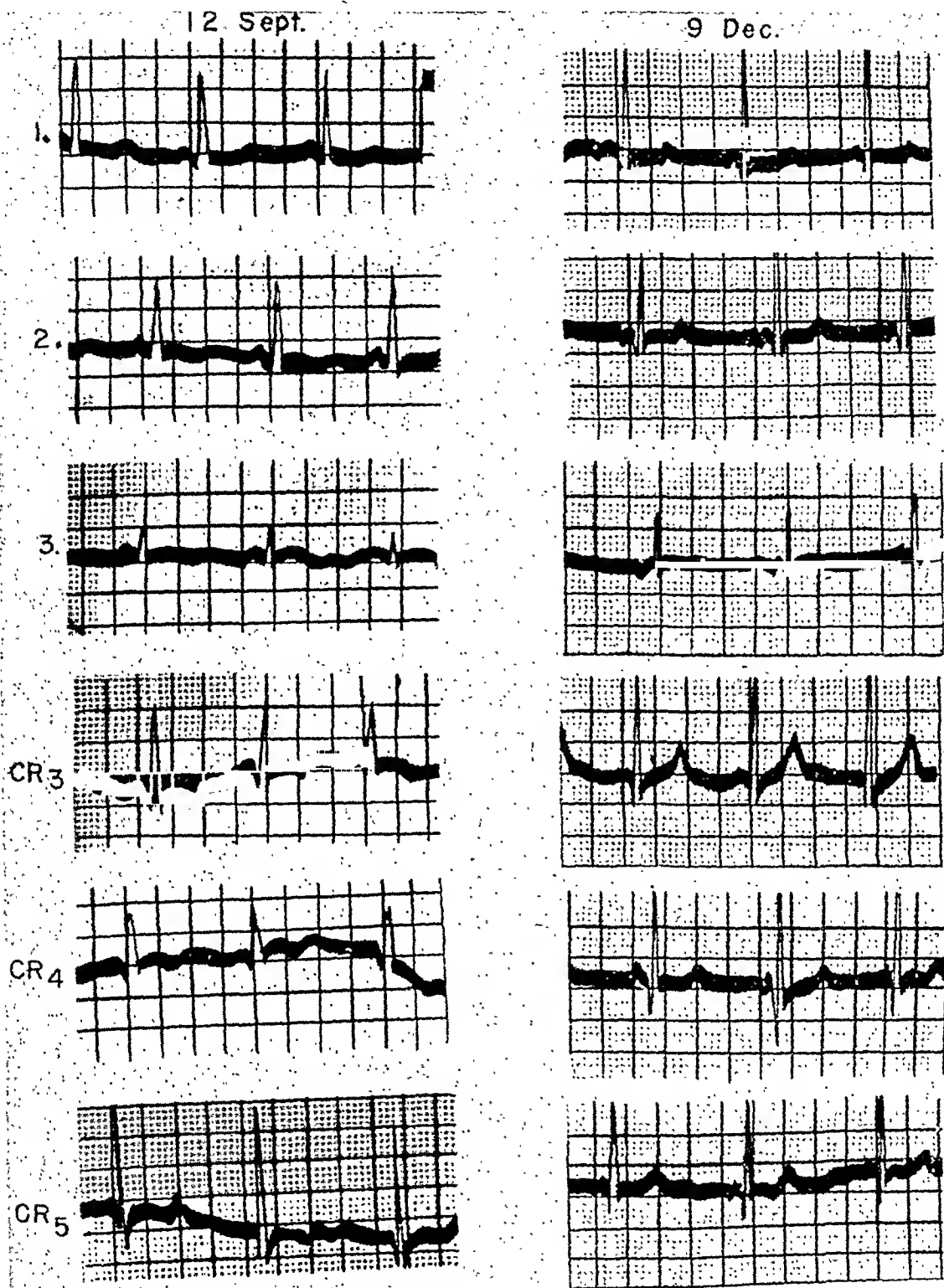


Fig. 2.—Definite myocarditis. Onset of cutaneous diphtheria July 5. Severity of lesions graded as 4 plus. Neuritis developed on the fifty-sixth day. The duration was one hundred forty-five days. Antitoxin was not given. Cardiac symptoms set in about the fiftieth day and consisted of dizziness and dyspnea. The electrocardiograph showed a rate of 75 to 85, with a nodal rhythm. The P-R interval was 0.08 to 0.11 second. There were intermittent inversions of the P waves in all leads. There were minor changes in the amplitude and configuration of the QRS complexes in serial tracings. The RS-T segments were slightly depressed in Lead I. The T waves were inverted in Leads II and III and the chest leads. In later tracings (e.g., December 9) the T waves became upright.

Criteria for the Diagnosis of Definite or Probable Myocarditis.—The diagnosis of myocarditis was considered certain in those patients in whom definite electrocardiographic abnormalities were observed in repeated tracings, with subsequent progressive changes toward normal. In three of the four patients so diagnosed there were corroborating clinical evidences of myocardial disease. Myocarditis was considered probable in patients in whom a definite and characteristic abnormality was observed in one tracing only, or in whom the electrocardiographic findings were highly suggestive of abnormality and showed progressive changes toward normal in repeated tracings. Clinical evidence of myocarditis was not present in these patients. Myocarditis was at first considered possible in a large number of patients, either on the basis of suggestive symptoms, tachycardia, or electrocardiographic findings (extra systoles, axis deviation, Q waves in Leads II and III, etc.) which suggested the possibility of abnormality. In most instances, the persisting and unchanging nature of these findings beyond the period when true myocarditis could be considered possible served to rule out organic cardiac disease. In seven patients, however, the possibility that a minimal myocarditis had been present could not be entirely excluded.

Relation of the Severity of the Cutaneous Disease to the Development of Myocarditis.—The 140 cases were graded according to their severity, depending upon the number and size of the cutaneous diphtheria lesions. Table I indicates the grade of severity of the cutaneous lesions in each of the patients with definite or probable myocarditis. It is apparent that definite myocarditis developed only in patients in whom the cutaneous disease was severe. In the patients with probable myocarditis the correlation is not so clear as in those with definite myocarditis.

TABLE I. THE SEVERITY OF THE SKIN LESIONS AND THE DEVELOPMENT OF MYOCARDITIS

Severity of skin lesions	4 plus	3 plus	2 plus	1 plus
Total number of cases	18	34	38	50
Definite myocarditis	3	1		
Probable myocarditis	1	1	1	

The Development of Neuritis With Relation to Myocarditis.—In the group of four patients in whom the diagnosis of myocarditis was definite, all but one, the patient who died, had neuritis, either severe or moderately severe. In two patients the symptoms of neuritis appeared at about the same time or slightly before there was evidence of cardiac involvement. In the third, neuritis had been present for twenty-eight days before the myocarditis was diagnosed on the sixtieth day of the cutaneous disease. In the group of three patients in whom the diagnosis of myocarditis was considered probable, only one developed neuritis, the onset of which occurred after the electrocardiographic abnormalities had disappeared. Thus, when myocarditis developed in cutaneous diphtheria, neuritis usually accompanied, preceded, or followed it.

Prevention and Treatment of Cardiac Complications.—In regard to these factors, we started with certain assumptions, and at the termination of the study our information had not greatly increased. For example, it was reasonable to

whom the diagnosis of myocarditis was made, and in these patients the P-R interval did not tend to change significantly as recovery progressed. In two patients with no other evidence of myocardial abnormality, a P-R interval of 0.24 second was found. These patients were considered to have possible myocardial complication. Tracings were taken repeatedly. After a number of weeks, despite the persistence of the long P-R interval, one of them was reconditioned and sent to duty; the other was reassigned on neuropsychiatric grounds.

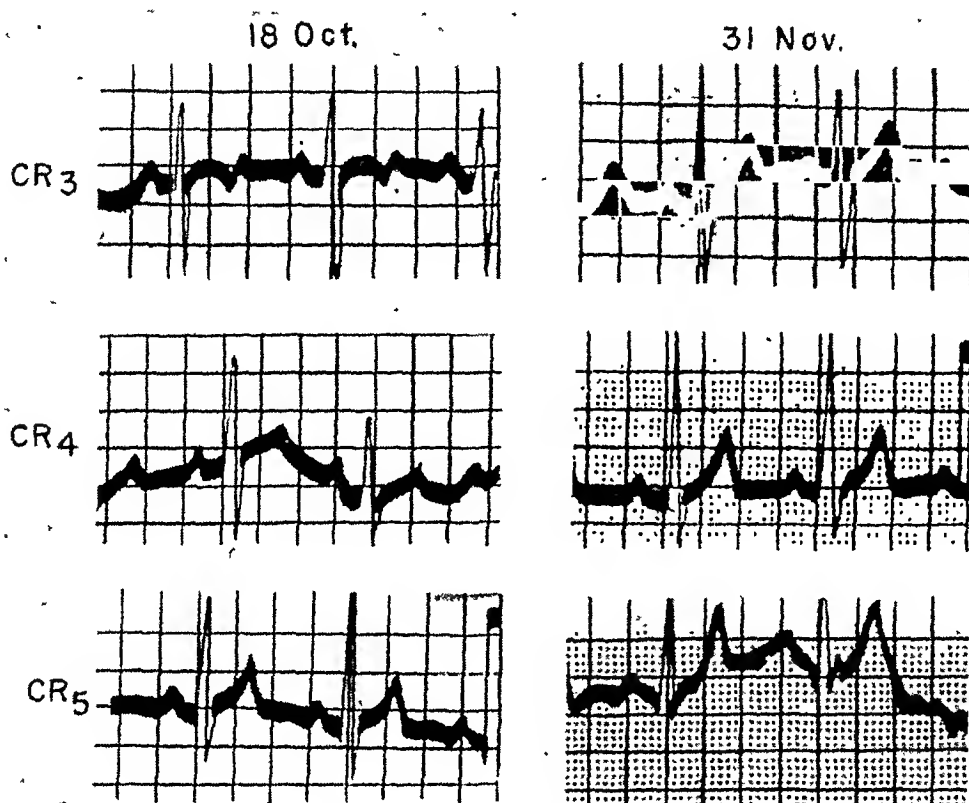


Fig. 4.—Probable myocarditis. Only the precordial leads are shown. Onset of cutaneous diphtheria September 8. Severity of lesions graded as 4 plus. There was no neuritis. Antitoxin was not given. There were no cardiac symptoms. The T waves in CR₃ were inverted in the first tracing, made on October 6 (twenty-eighth day). T-wave changes were most pronounced on October 18, less marked on November 8, and normal on November 24 (seventy-fifth day). T₁ was flat in the tracing of October 6 and became progressively higher during the period of the return to normal of the T waves in CR₃. The tracing was otherwise normal. The duration of electrocardiographic abnormality was forty-seven days.

We doubt that this finding was a manifestation of diphtheritic myocarditis. In the patient who died, P waves could not be definitely identified. One patient with definite myocarditis had a consistently short P-R interval with intermittent P wave inversion in all leads. (4) Abnormalities in the QRS complex were not striking. The amplitude was a little low in some instances and pronouncedly so in the patient who died. He also had very abnormal QRS complexes in the chest leads. Intraventricular conduction defects were not observed. (5) The most marked abnormalities were in the T waves, especially in Lead CR₃. Depression or frank inversion of the T wave in this lead was the one consistent finding, occurring in all of the patients in whom the diagnosis was made with the exception of the one who died. Figs. 1, 2, 3, and 4 are representative tracings from the patients in this series.

relation of cardiac to neuritic complications. It was the general impression that antitoxin would be of little or no benefit except in the earliest stages of the skin disease.

As a result of our experience with 140 cases, the following impressions have been formed regarding cardiovascular management:

1. Patients in whom the diagnosis of cutaneous diphtheria is suspected should be immediately evacuated to a general or station hospital where adequate facilities for isolation, treatment, and study (including electrocardiography) are available.

2. Among the patients whose skin lesions were mild or minimal, prolonged confinement to bed resulted in more psychological and physical disability than was warranted by the potential danger of myocarditis. This selected group should be given freedom of the ward, cardiac symptoms should be carefully investigated, and tracings should be taken about every two weeks until three weeks after the cutaneous lesions have begun to heal. If no evidence of abnormality is then found, further cardiac study is unnecessary.

3. Patients with severe cutaneous diphtheria should be confined to bed and closely observed. Tracings should be made every week or ten days until about seven weeks after the onset of the lesions. Periodic tracings should be made for an even longer period if the activity of the cutaneous lesions is unusually prolonged. If at that time there is no evidence of myocarditis, activity may be resumed. A final tracing should be taken at about the tenth week.

4. In regard to the use of antitoxin, further information is needed. The possibility has been considered that large doses (200,000 to 400,000 units) might have more evident beneficial effects than doses of 20,000 or 40,000 units.

Comparison With the Myocardial Complications of Faucial Diphtheria.—The myocarditis we have observed as a sequel to cutaneous diphtheria resembles that which complicates the faucial form in several respects. In either instance the signs and symptoms of severe myocarditis are similar and dramatic, but in the milder forms are not striking.^{3-5, 8} When death does not occur in the acute phase of the complication, the prognosis for ultimate complete recovery is excellent.⁶ The pathologic findings in our fatal case resembled those described in the myocarditis of faucial diphtheria.^{7, 8} It is of especial interest to compare our series of 140 cases of cutaneous diphtheria with the series of 140 cases of faucial diphtheria which Burkhardt, Eggleston, and Smith⁸ followed with especial reference to cardiac and neurological complications. Twenty-three of their patients developed T-wave changes, principally during the second and third weeks of the illness. Similar T-wave changes developed in six of our patients between the fourth and seventh weeks. In their series, 17 patients showed conduction defects between the fifth and thirteenth days of the diphtheria; in our one fatal case, in which the myocarditis developed on the thirty-eighth day, an A-V dissociation may have been present. Fourteen fatalities occurred in their series, one occurred in ours. In both series, neuritis was associated with myocarditis in high incidence. It would thus appear that the myocarditis which follows cutaneous diphtheria is essentially identical with that

assume that any local or general therapeutic measures which would reduce the severity and duration of the cutaneous lesions would also reduce the frequency of the complications. These therapeutic methods are discussed in detail elsewhere.¹ It may be stated in brief that the most important factors were rest, local hygiene, and the prompt injection of antitoxin. A variety of local medications as well as systemic sulfonamides and penicillin were tried with different results.

Of the seven patients who developed definite or probable myocarditis, only one had received antitoxin. This was a patient in whom the diagnosis of probable myocarditis was made only two days after the serum was injected. Despite this observation, no conclusion regarding the direct efficacy of antitoxin as a prophylactic agent can be drawn; many other considerations were involved. In the early cases, in which antitoxin was rarely given and limitation of activity was not enforced, the skin lesions were generally much more severe than the later cases in which treatment was noneffective; it was from this early group that six of the seven cases of myocarditis were derived. Likewise, myocarditis was never seen to develop in any patient after he had been restricted to bed; but for the same reasons, the virtue of this measure is difficult to assess.

Six of the seven patients with myocarditis recovered. The only therapeutic measure employed was bed rest until all evidences of abnormality had disappeared. None of these patients at any time appeared to be in serious danger from his cardiac disease; therefore, a conservative policy seemed justified and experimentation contraindicated. In the patient who died, the diagnosis was not made until about eighteen hours before death; bed rest, morphine, and oxygen were the measures used, but in view of the condition of the myocardium at autopsy, it seems doubtful that any therapy instituted at that late date would have influenced the outcome.

Ultimate Disposition.—Of the four patients in whom the diagnosis of myocarditis was definite, one died, one was reassigned to noncombat duty, and two were returned to the United States, primarily because of neuritic rather than cardiac complications. Of the three patients in whom the diagnosis was probable, one returned to full combat duty, one was reassigned to noncombat duty because of indolence of his skin lesions, and one was returned to the United States for reasons unrelated to his diphtheria. In all, no patient was confined to the hospital more than one hundred fourteen days for cardiac study or treatment; some remained longer, but for other reasons.

Discussion of the Management.—At the beginning of the epidemic we were not sure that we were dealing with cutaneous diphtheria. The dermatologist had suspected the possibility, yet all cultures had been negative. The death of a patient from a cardiac complication immediately focused our attention on the etiology, and gave rise to a strict set of rules for management and careful cardiac study of all cases. Although there is a great deal of literature on postfaucial diphtheritic myocarditis, very little information was available to us about the cardiac complications of cutaneous diphtheria. Nothing was known concerning the incidence, time intervals, correlation with severity of cutaneous lesions, or

damage to the myocardium and consider them to have little or no prognostic value. We are not entirely in agreement with this opinion, in view of the clinical evidence of heart disease in three of our patients in whom the electrocardiographic changes were of the T-wave type. Our view that T-wave changes do have prognostic value is supported by an example of severe heart disease following faucial diphtheria. The symptoms and signs in this patient resembled those of a severe coronary occlusion. The first tracings taken showed only marked RS-T segment and T-wave abnormalities, but intraventricular conduction defects developed a few days later (Fig. 5). We feel that the RS-T segment and T-wave abnormalities are the result of an early or mild myocardial involvement and are potential precursors of later, more serious involvement.

SUMMARY

1. The myocardial complications which developed in a group of 140 patients with cutaneous diphtheria have been considered.

2. Shortly after cutaneous diphtheria was first observed in this hospital we became impressed with the gravity of the myocardial complications, and measures were instituted in an effort to recognize this complication early and to prevent death from this cause. The measures adopted may have been more stringent than necessary.

3. Definite myocarditis appeared in four patients, one of whom died. The diagnosis was considered probable in three additional patients, an incidence of 5 per cent. In seven other patients the diagnosis could not be excluded entirely.

4. The symptoms, signs, laboratory studies, and electrocardiographic findings in these patients are discussed.

5. Cardiac complications developed from the fourth to seventh week after the onset of the skin lesions. Their duration was from one to three months. All patients who survived showed no evidence of cardiac abnormality after four and one-half months from the onset of the skin lesions. The electrocardiograph is an essential in the diagnosis and evaluation of the myocarditis.

6. A definite parallel relationship existed between the severity of the cutaneous lesions and development of cardiac complications. Of 18 patients with very severe cutaneous diphtheria, four (22 per cent) developed myocarditis; whereas the complication did not appear in any of the 50 patients in whom the cutaneous lesions were mild.

7. Neuritis developed as a complication in the three patients with definite myocarditis who survived, and in one of the three patients in whom the diagnosis of myocarditis was probable. The onset of neuritis either preceded, or coincided with, or followed the onset of the myocarditis.

8. It is concluded that myocarditis is an infrequent complication of cutaneous diphtheria, but one which must be especially considered in any patient in whom the degree of cutaneous involvement is severe.

The author is indebted to Colonel Francis C. Wood for his many helpful suggestions and to First Lieutenant Thelma Cline for invaluable technical assistance in the course of this study.

which follows faucial diphtheria, but is a less frequent complication and one which develops at a later period after the onset of the infection.

Ball⁹ has described the evolution of RS-T segment and T-wave changes in two cases of myocarditis after faucial diphtheria. These patients showed no clinical evidence of heart disease. Burkhardt, Eggleston, and Smith⁸ consider the T-wave changes to be the result of intoxication rather than of structural

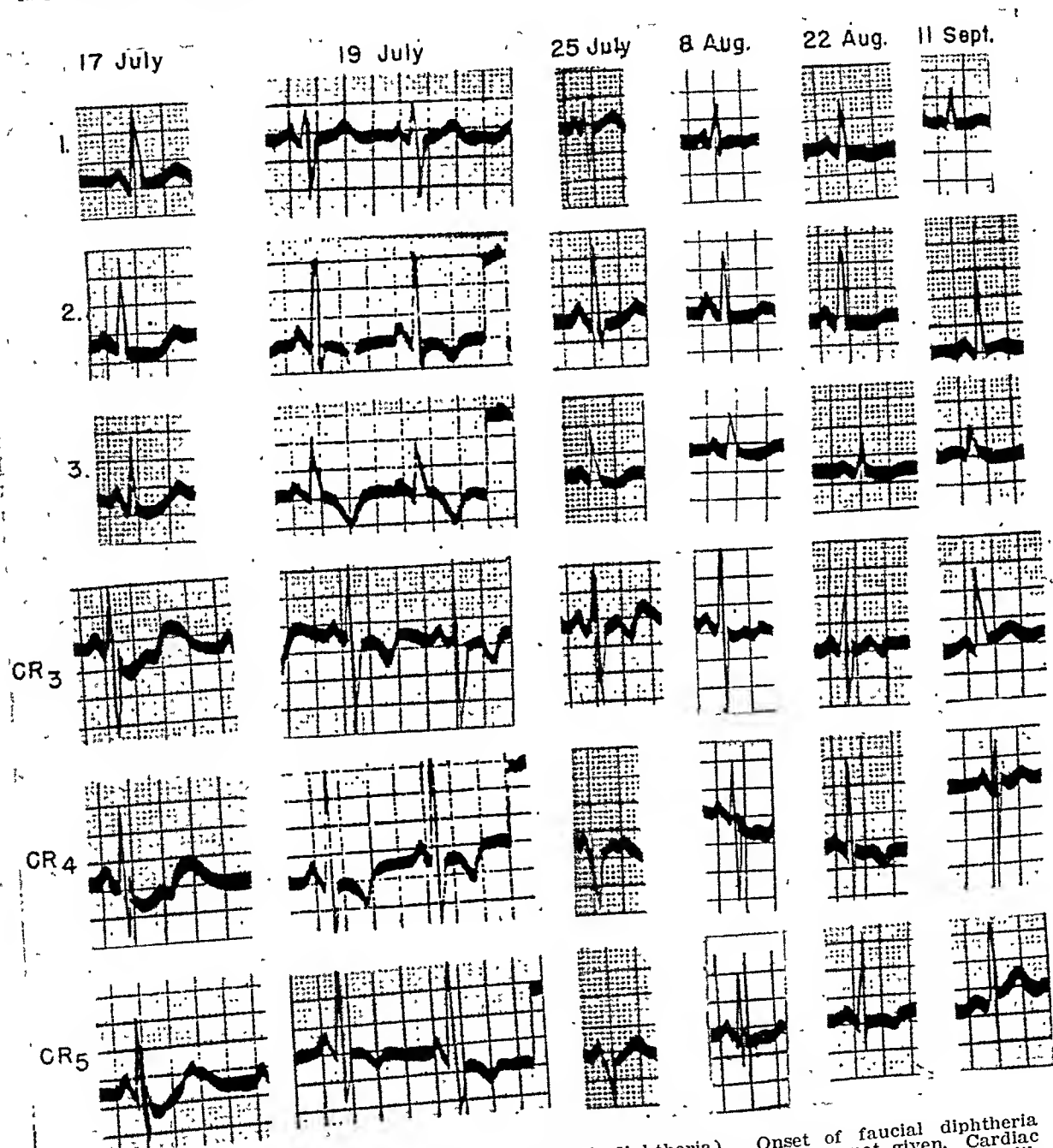


Fig. 5.—Definite myocarditis (after faucial diphtheria). Onset of faucial diphtheria June 15. Onset of severe neuritis about forty-eighth day. Antitoxin was not given. Cardiac symptoms consisting of severe substernal pain and dyspnea set in about the twenty-fifth day. The electrocardiograph showed a rate of 80 to 90, with a normal sinus rhythm. The P waves were large and peaked. The P-R interval was 0.14 to 0.17 second. The QRS complexes were widened and slurred, with a maximum interval of 0.11 second. The early tracings showed depression of the R-ST segment in all leads. The T waves were bizarre and changed rapidly. There was a progressive improvement in the tracing, which appeared relatively normal on September 11 (eighty-eighth day).

THE PRESENCE AND PATHOGENESIS OF ENDOCARDIAL AND SUBENDOCARDIAL DEGENERATION, MURAL THROMBI, AND THROMBOSES OF THE THEBESIAN VEINS IN CARDIAC FAILURE FROM CAUSES OTHER THAN MYOCARDIAL INFARCTION

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FIBROSIS or fibrinoid changes of the endocardium, with or without a leucocyte infiltration, and hydropic degeneration of the subendocardial myocardium are commonly found in noninfarcted hearts of patients having signs and symptoms of congestive heart failure, regardless of the etiology of the failure. Much less commonly, in addition to the endocardial fibrosis and subendocardial hydropic degeneration, ventricular mural thrombi and thromboses of the thebesian veins may occur. In the following two case reports all of the aforementioned morphologic changes were present.

CASE REPORTS

CASE 1.—

Clinical History.—On Jan. 16, 1945, the patient, a 29-year-old white man, was admitted to the hospital complaining of hoarseness, pain on swallowing, and persistent cough. In March, 1943, he had a brief episode of hoarseness. The hoarseness recurred in June, 1944, and persisted. In December, 1944, he began to cough and lose weight. The physical examination revealed hoarseness and diffuse audible pulmonary râles. A laryngoscopic examination showed swelling, infiltration, and ulcerations of both false and true vocal cords. The complete blood count, sedimentation rate, and urinalysis were within normal limits. The Kahn test for syphilis was negative. The sputum was positive for acid-fast bacilli. An x-ray film of the chest revealed widely disseminated densities throughout both lung fields. Planigraphic films showed two small cavities in the left upper lobe.

The patient was put on bed rest and given a high-caloric, high-vitamin diet. He was uncooperative in the maintenance of bed rest and voice rest. His symptoms became progressively worse and there was progressive weight loss. He died with manifestations of circulatory failure on April 16, 1945.

Clinical Diagnosis.—Bilateral, pulmonary, tuberculosis, with cavitation in left upper lobe; and tuberculous laryngitis.

Necropsy Abstract.—The left lung weighed 1,050 grams and the right weighed 1,308 grams. Both lungs were heavy and firmly consolidated. In the left lung near the medial border in the upper lobe there were two cavities, each measuring 3 cm. in diameter. They contained thin reddish gray fluid. The walls were thin. On section, the cut surfaces of the lungs were everywhere studded with innumerable small white tubercles. These were fairly uniform in size, averaging about 4 mm. in diameter. Most were moderately hard and stood out from the cut surface. A few yellowish caseous areas were noted in the apices and in the hilar region. These areas measured 1 to 2 cm. in diameter. A few dense strands of grayish blue fibrous tissue were noted running through the lung in the same regions. A moderate amount of turbid grayish red fluid flowed from the cut surface.

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Fig. 2.—Case 1. Photomicrograph of right ventricular myocardium showing thrombosed thebesian vein. ($\times 100$.) (U. S. Army Medical Museum, Negative 89592.)

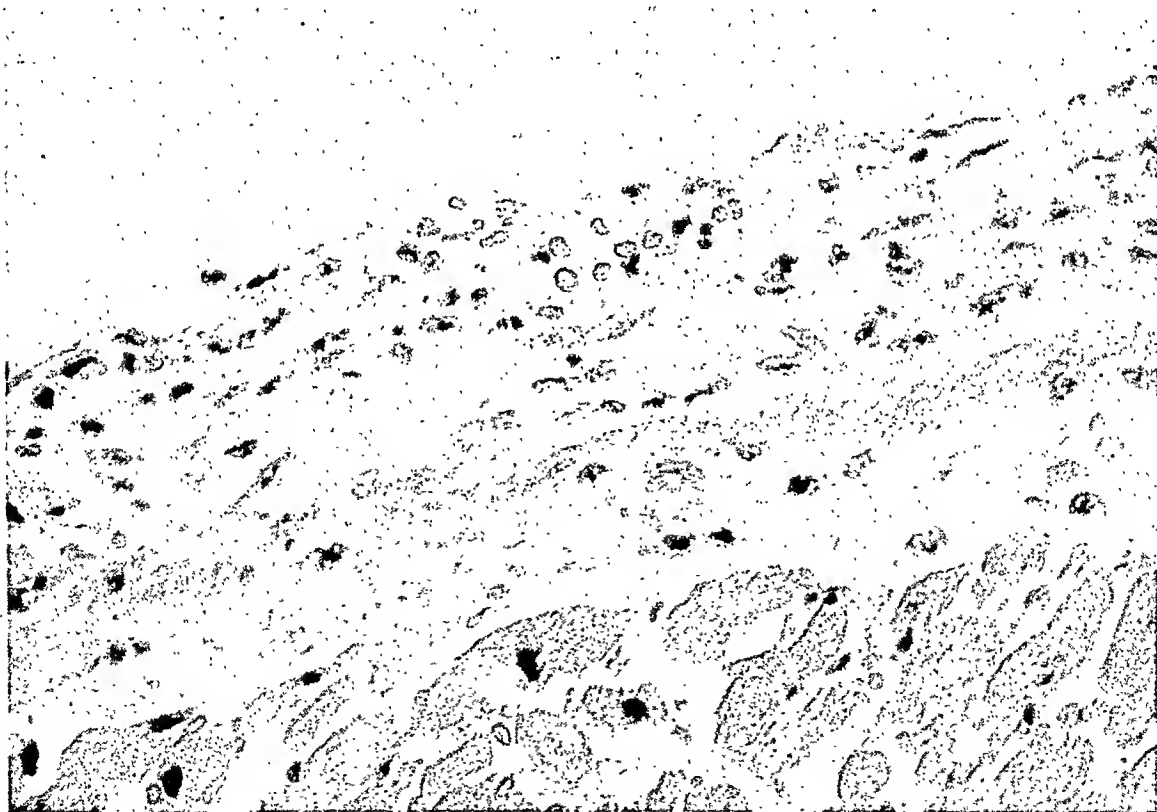


Fig. 3.—Case 1. Photomicrograph showing widening of the endocardium of the right ventricle, fibrinoid change of the connective tissue, and infiltration by polymorphonuclear leucocytes. ($\times 700$.) (U. S. Army Medical Museum, Negative 89590.)

The heart was slightly enlarged; its weight was 480 grams. There was distinct dilatation of the right side. The epicardium was smooth and intact and contained a moderate amount of pale yellow fat. The endocardium of the left auricle and ventricle was smooth and translucent. The foramen ovale was closed. The right auricle and ventricle were filled with a large soft currant-jelly clot. On removing this clot, numerous gray rounded mural thrombi were seen to almost completely line the right ventricle. These thrombi were firmly adherent to the endocardium. They were lodged between the trabeculae carneae, and their smooth, rounded surfaces projected slightly into the lumen of the chamber. A moderate number of similar thrombi, although smaller in size, were found in the right auricle. The valves were all normal. The aortic cusps were thin and accurately apposed at the commissures. The myocardium presented a normal pattern of fibers. It was pale gray red in color. The left and right ventricular walls measured 1.3 and 0.8 cm., respectively, in thickness. The increase in the size of the heart was mainly accounted for by the right ventricular hypertrophy. The coronary arteries presented clear lumina of good caliber in all main branches. Their intimal surfaces were smooth and white.

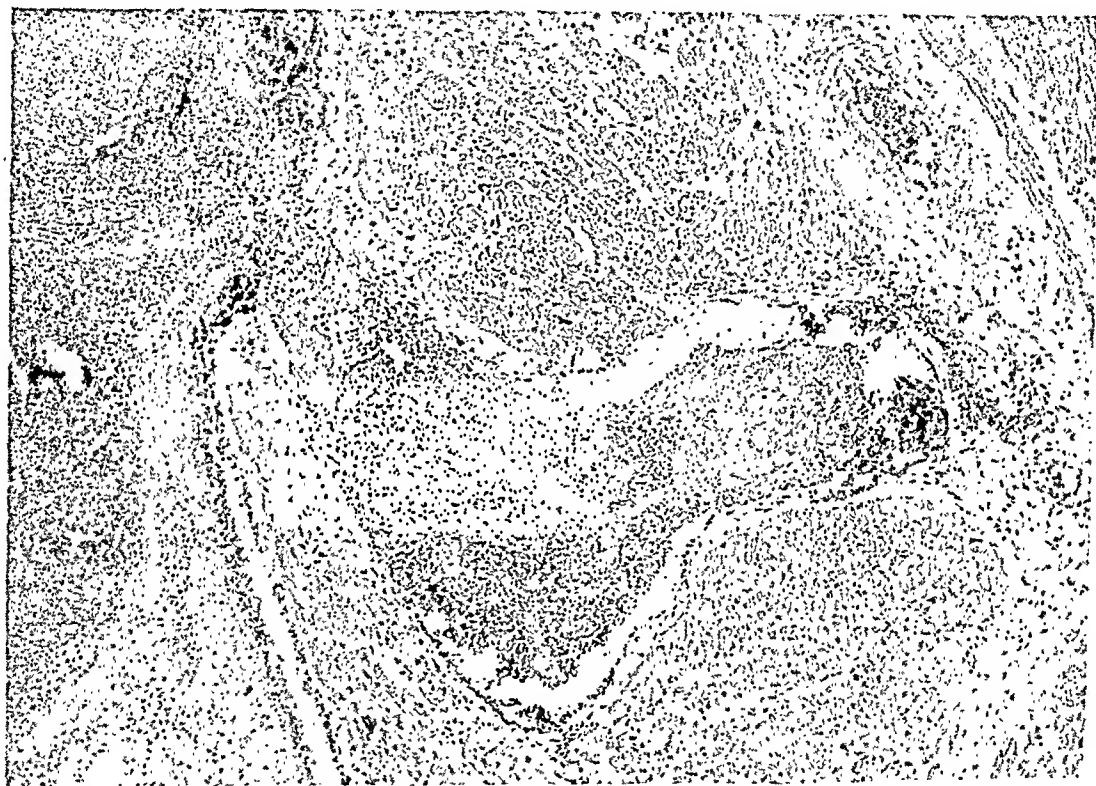


Fig. 1.—Case 1. Photograph of right ventricle showing the mural thrombosis in the interspaces of the trabeculae carneae and the thrombosis of a thebesian vein. ($\times 100$). (U. S. Army Medical Museum, Negative 89589.)

On the anterior wall in the upper portion of the esophagus there were irregular ulcerations measuring 2 to 4 mm. in diameter. The larynx showed marked ulcerations of both the true and false vocal cords. The mucosal surfaces were covered with irregular shallow ulcerations. Similar ulcerations were present on the posterior surface of the epiglottis.

Microscopically, the lesions of the lungs, epiglottis, and esophagus all showed the typical morphologic changes of tuberculosis. Acid-fast rods were easily demonstrated in the various lesions. No appreciable sclerosis of the pulmonary vessels was noted. The histologic sections through the right ventricle revealed the mural thrombi to be made up of areas of platelets mixed with polymorphonuclear leucocytes, alternating with areas of erythrocytes. A considerable proportion of the erythrocytes was well preserved. Thrombi of the same structure blocked and massively distended the thebesian veins. Some smaller

CASE 2.—

Clinical History.—The patient, a 49-year-old white man, was admitted to the hospital on Sept. 27, 1943. He had been hospitalized fourteen times for congestive failure. His first hospitalization was in 1930, when he gradually developed edema, ascites, dyspnea, and palpitation. These symptoms were at first mild but gradually increased in severity. Previous to his first hospitalization he had been well except for gonorrhea in 1915 and recurrent attacks of tonsillitis, the last of which occurred in 1932. At the time of his first cardiac episode in 1930, after being hospitalized for sixteen weeks, he recovered sufficiently to return to military duty. In 1932, symptoms of cardiac decompensation recurred. This time he was given a medical discharge after fourteen years of service in the Army. Between 1932 and 1940 there were repeated episodes of heart failure, and hospitalization was required six times during this period.

On admission to the hospital in 1940, his chief complaints were dyspnea and orthopnea following an acute upper respiratory infection of seven days' duration. Physical examination revealed a blood pressure of 110/90 and evidence of pulmonary edema. There was a 2 plus albuminuria and a 2 plus pyuria. The blood nonprotein nitrogen was 30 mg. per 100 cubic centimeters. A diagnosis of "myocarditis with congestive heart failure" was made. The patient was treated with digitalis, rest, and diuretics. He was discharged as improved.

He was readmitted to the hospital in October, 1941, complaining of dyspnea, anorexia, cramps in the leg muscles, vertigo, and syncope. The blood pressure was 102/88. The heart was not enlarged. No cardiac murmurs or disturbances in the heartbeat were present. Gastrointestinal roentgenographic studies were normal. There was a 1 plus albuminuria. The diagnoses of generalized arteriosclerosis and mild cardiac decompensation were made. He was treated for congestive heart failure, from which he again recovered. He was readmitted to the hospital on Dec. 30, 1941, because of shortness of breath, edema of lower abdomen and legs, dysuria, and epigastric distress. There were no chest pains. Physical examination revealed distended neck veins, evidence of pulmonary congestion, and slight enlargement of the liver. The heart was enlarged, maximum intensity of the apex heartbeat being in the sixth intercostal space in the anterior axillary line. The pulmonary second sound was accentuated. There was moderate arteriosclerosis; the blood pressure was 120/90. In spite of the fact that typical murmurs were not heard and in spite of the fact that an x-ray film of the chest was not confirmatory, a diagnosis of mitral stenosis was made. The complete diagnosis on discharge was mitral stenosis and relative mitral insufficiency, generalized arteriosclerosis, hypertrophy of left ventricle, first degree auriculoventricular block, myocardial degeneration, and myocardial insufficiency.

The twelfth hospital admission for congestive heart failure took place on Oct. 10, 1942. One examiner reported the following: "This patient is a classical mitral stenosis type with right-sided failure, which goes into decompensation repeatedly." The maximum intensity of the apex beat was reported in the sixth intercostal space at the anterior axillary line. The heart sounds were diminished in intensity. The pulmonary second sound was accentuated. There was a rough, short presystolic murmur in the mitral area, with the suggestion of a diastolic murmur at the base of the heart. The heart rate was 72 per minute and the rhythm was regular. An electrocardiogram showed P-R intervals of 0.22, 0.26, and 0.24 second. After digitalization and rest the symptoms of cardiac failure disappeared.

The patient was readmitted to the hospital for the thirteenth time on Dec. 9, 1942, because of the recurrence of congestive heart failure. Examination revealed enlargement of the liver, ankle edema, distention of neck veins, and arteriosclerosis of the peripheral vessels. The blood pressure was 120/70. The electrocardiogram showed persistent first-degree auriculoventricular block, intraventricular block, and T-wave changes indicating diffuse myocardial damage. A presystolic apical murmur, low-pitched and rumbling, and a high-pitched diastolic apical murmur were heard. Enlargement of the left ventricle and left auricle was present. The congestive heart failure responded to digitalis, rest; and diuretics.

The fourteenth and last admission took place in September, 1943. Physical examination showed the skin to be dry, cool, and slightly cyanotic. There was evidence of intrapulmonary

thrombi were found in veins deep in the myocardium and even in the epicardium. In many places the endocardium itself was infiltrated with polymorphonuclear leucocytes. Under such an infiltrated area, a thin layer of subendocardial myocardium stained a deep pink, and showed pyknotic nuclei. Elsewhere some of the subendocardial muscle fibers were swollen and pale staining. There was a diffuse sprinkling of lymphocytes in many areas of the myocardium. These were accompanied by occasional polymorphonuclear leucocytes and large mononuclear cells. Small foci of these cells were occasionally seen beside blood vessels. The right auricle showed the same changes as the right ventricle. The left ventricle showed only slight swelling and vacuolization of the subendocardial muscle fibers.



Fig. 4.—Case 1. Photomicrograph showing two thrombosed thebesian veins of the right ventricle. ($\times 69$.) (U. S. Army Medical Museum, Negative 89591.)

Anatomic Diagnosis.—Bilateral pulmonary tuberculosis with cavitation of the left upper lobe; tuberculosis of the larynx and esophagus; degenerative changes in the endocardium of the right auricle and ventricle, with mural thrombi; thromboses of the thebesian veins of the right auricle and ventricle; hypertrophy and dilation of the right ventricle; bilateral lobular pneumonia.

Comment.—This case of rapidly progressive pulmonary tuberculosis was already far advanced when medical attention was sought. The patient's terminal signs were those of circulatory failure. At autopsy, tuberculosis was found to involve principally the lungs and larynx. The right side of the heart was dilated and lined with mural thrombi. There was fibrinoid degeneration and leucocytic infiltration of the endocardium in these chambers. The thebesian veins were dilated and freshly thrombosed. Since the pulmonary vessels were normal, the dilatation of the heart was presumably the result of a toxic effect of the infection on the myocardium.



Fig. 5.—Case 2. Photomicrograph of right ventricular myocardium showing marked endocardial fibrosis and hydropic degeneration of the subendocardial myocardium. ($\times 130$.) (U. S. Army Medical Museum, Negative 87901.)



Fig. 6.—Case 2. Photomicrograph of left ventricle showing mural thrombus formation and endocardial fibrosis. In the subendocardial myocardium there is an inflammatory cell infiltration and extensive myomalacia with replacement fibrosis. The islands of surviving muscle fibers show marked hydropic degeneration. The identity of the thebesian veins is lost in the fibrotic tissue. ($\times 130$.) (U. S. Army Medical Museum, Negative 87904.)

and of pleural fluid, moderate arteriosclerosis, absence of pulsation of the dorsalis pedis arteries of both feet, moderate bilateral varicosities, and moderate ankle edema. The blood pressure was 108/76. The heart was markedly enlarged to the left, with the maximum intensity of the apex beat in the sixth intercostal space at the anterior axillary line. There was an apical systolic murmur, soft and blowing. The neck veins were distended. Slight enlargement of the liver was noted. No ascites was present. On this admission albuminuria and moderate secondary anemia were present. The electrocardiogram revealed evidence of severe myocardial damage, first degree auriculoventricular block, and left axis deviation. An x-ray film of the chest showed left ventricular enlargement and pulmonary congestion. During this admission the patient ran the gamut of all phases of congestive heart failure, showing nearly every type of cardiac arrhythmia and heart block. He had difficulty in voiding and required catheterization. Hemoptysis and leucocytosis appeared during the final two days. He expired at 11:05 A.M., Nov. 19, 1943.

Clinical Diagnosis.—Heart disease. (A) Etiological: (a) rheumatic fever, quiescent; (b) moderate generalized arteriosclerosis. (B) Structural: mitral stenosis and insufficiency; hypertrophy and dilatation of left and right ventricles; myocardial degeneration and insufficiency; pulmonary infarction. (C) Physiologic: auricular fibrillation; auricular paroxysmal tachycardia; A-V and bundle branch block.

Necropsy Abstract.—The heart weighed 485 grams. All chambers showed moderate hypertrophy and marked dilatation. The right auricle was especially dilated and the great veins leading into it were distended with blood. On the anterior surface of the left ventricle was an irregular milky white plaque about 3 cm. in diameter. The epicardium was otherwise smooth and intact; it contained a moderate amount of fat. Adhering to the endocardial surfaces of both ventricles, especially between the trabeculae carneae, were numerous mural thrombi. Most of these were red and showed fine white layers on section. They measured up to 3 cm. in diameter. Some of the thrombi were grayish brown and showed slight central softening. Both of the auricular appendages were filled and distended with thrombi. The tricuspid valve measured 12.5 cm.; the pulmonic, 8 cm.; the mitral, 10 cm.; and the aortic, 7 centimeters. The tricuspid leaflets were thin, delicate, and translucent; the chordae tendineae attaching to them were thin and discrete. The pulmonic valves appeared normal except for distinct dilatation of the ring. The mitral leaflets were of normal configuration, thin, and delicate; their chordae tendineae were thin and showed no fusions. The aortic cusps were thin and accurately apposed at the commissures. The myocardium was brownish red with a striking yellowish gray cast, and of rather flabby consistency. The fibers were poorly defined. Scattered through the myocardium were tiny translucent gray areas measuring 1 mm. or less in diameter. These were located principally in the regions beneath the mural thrombi. In the region of the apex, the wall of the left ventricle was thinned, measuring in places no more than 5 millimeters. In this area strands of gray fibrous tissue were noted in the myocardium. The endocardium over these areas was thick, white, and fibrous. Elsewhere the left ventricular wall averaged 1.4 cm. in thickness, while the right ventricular wall averaged 0.4 centimeter. All principal branches of the coronary arteries were of large caliber; there were no occlusions. The walls of these vessels were elastic, and their intimal surfaces were white and perfectly smooth.

Microscopic sections through the mural thrombi showed striking degeneration and fibrosis of the endocardium and subendocardial myocardium beneath the thrombi. In the trabeculae carneae the muscle fibers were almost completely replaced by loose fibrous tissue containing considerable numbers of young fibroblasts. The outlines of groups of muscle fibers were represented here and there by fibrinoid material staining bright pink. The fibrous tissue was highly vascular and contained numerous large capillaries, which were for the most part congested. There were many ecchymoses. Numerous large and small mononuclears and pigment-filled mononuclear macrophages were scattered through the fibrous tissue. There were a few polymorphonuclear leucocytes. The mural thrombi were densely adherent to this degenerate endocardium and subendocardium. The endothelium was entirely destroyed. The capillaries and fibrous tissue grew from the endocardium into the thrombi at various points.

TABLE I

CASE RACE SEX AGE (YR.)	CARDIAC PATHOLOGY	DURATION OF VENTRICULAR FAILURE	ETIOLOGY
A-41 White male 51	Weight 555 grams. Marked hypertrophy and dilatation of right and left ventricles. Slight to moderate coronary arteriosclerosis. Slight myocardial fibrosis. Slight subendocardial hydropic degeneration and fibrosis of the interventricular septum	2 weeks	Hypertensive heart disease
A-14 White male 42	Weight 470 grams. Slight right- and left-sided hypertrophy and dilatation. No appreciable coronary sclerosis. Rheumatic panmyocarditis. Myocardial fibrosis. Marked left ventricular subendocardial hydropic degeneration	1 month	Rheumatic heart disease
A-11 White male 50	Weight 470 grams. Dilatation and hypertrophy of right ventricle, dilatation of left ventricle. Marked coronary sclerosis. Myocardial fibrosis. Marked left ventricular subendocardial hydropic degeneration and marked fibrosis	1 year	Coronary sclerotic heart disease
A-12 White male 66	Weight 720 grams. Right- and left-sided hypertrophy and dilatation. Slight to moderate coronary sclerosis. Slight left ventricular myocardial fibrosis. Left ventricular subendocardial necrosis and fibrosis	2 years	Hypertensive heart disease
A-24 White male 70	Weight 560 grams. Marked left-sided hypertrophy and dilatation. Coronary arteriosclerosis. Left ventricular myocardial fibrosis. Extreme left ventricular subendocardial hydropic degeneration and necrosis. Thebesian vein thromboses, left ventricle. Mural thrombi, left ventricle	8 years	Coronary sclerotic heart disease
A-7 White male 46	Weight 750 grams. Hypertrophy and dilatation of all chambers. Marked coronary arteriosclerosis. No coronary occlusion. Left ventricular endocardial fibrosis. Slight hydropic degeneration of subendocardial myocardium of left ventricle. Mural thrombi left ventricle and right auricular appendage. Thromboses of thebesian veins, left ventricle	6 months	Hypertensive heart disease
A-34 White male 76	Weight 730 grams. Hypertrophy and dilatation of left ventricle. Subendocardial hydropic degeneration of left ventricle. Marked sclerosis of coronary vessels	3 years	Hypertensive heart disease, coronary sclerosis
A-29 White male 73	Weight 570 grams. Left ventricular hypertrophy and dilatation. Slight coronary arteriosclerosis. Fibrinoid necrosis of endocardium of left ventricle. Hydropic degeneration of subendocardial myocardium of left ventricle	6 days	Hypertensive heart disease

The thrombi seemed to be of varying ages; some appeared to be fairly recent. Large groups of erythrocytes in various stages of preservation alternated with areas of fibrin and polymorphonuclear leucocytes. In the other portions of the thrombi dense strands of condensed fibrin threads staining bright pink were noted. Practically all of the trabeculae carneae were degenerated. In places other than the trabeculae carneae, the degeneration usually extended for variable distances below the endocardium. Organized thrombi within their lumina had converted the thebesian veins into solid cords of fibrous tissue. The coronary arteries appeared to be normal. The muscle fibers elsewhere in the myocardium were in some instances large and pale-staining. There appeared to be a distinct increase in the number of capillaries; many were congested. Sections through the auricles showed their endocardium practically covered with thrombi, the majority of which were rather recent. The subendocardial myocardium showed degenerative changes essentially similar to those in the ventricles except that the degeneration was present only in scattered areas and involved only a very thin layer of myocardium. Several of the larger myocardial veins contained thrombi, presumably the result of propagation from the thebesian veins. The remaining findings are listed in the anatomic diagnoses.

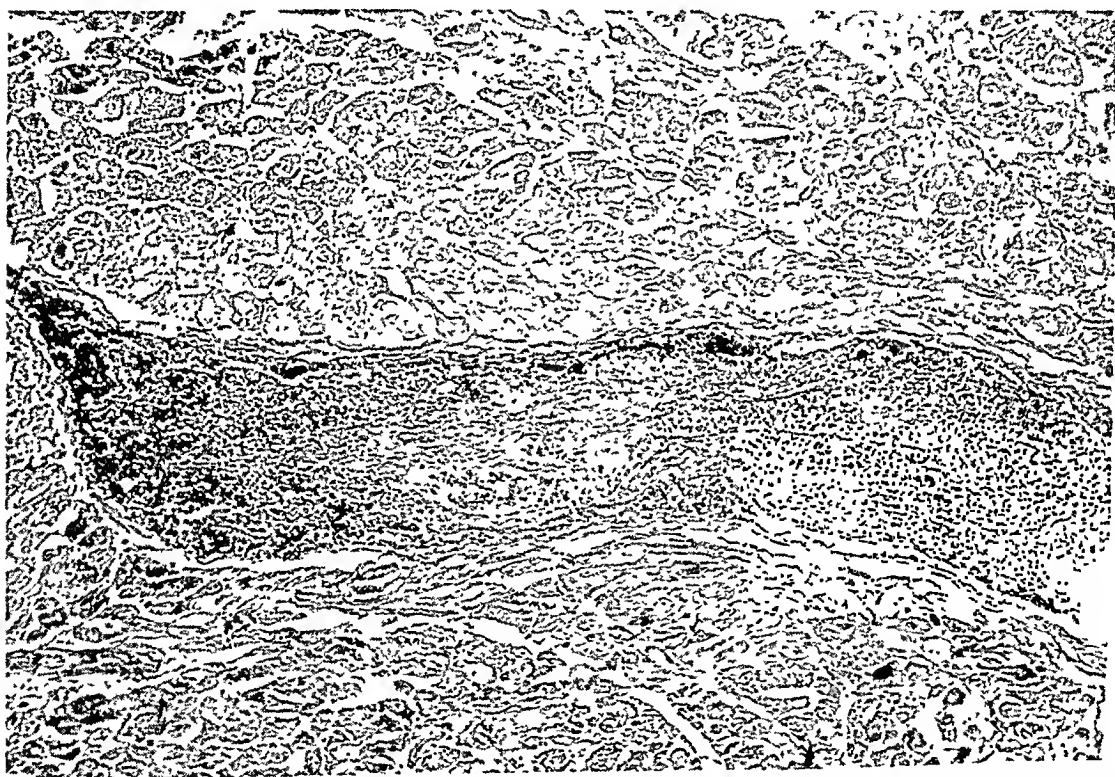


Fig. 7.—Case 2. A thrombosed venous sinus in the left ventricular myocardium. Note the hydropic degeneration of the myocardial fibers adjacent to one side of the vessel. ($\times 130$.) (U. S. Army Medical Museum, Negative 87902.)

Anatomic Diagnosis.—Degeneration and fibrosis of endocardium and subendocardial myocardium; mural thrombi in all cardiac chambers; organized thromboses of the thebesian veins and recent thromboses of larger myocardial veins; cardiac hypertrophy and dilatation; multiple bilateral pulmonary infarcts and infarcts of kidneys and spleen; congestion, necrosis, and fibrosis of the liver; fibrosis of the lungs; moderate generalized arteriosclerosis.

Comment.—This case was characterized by many bouts of cardiac failure necessitating fourteen hospitalizations over a period of thirteen years. At autopsy the heart weighed 485 grams. There was no evidence of rheumatic endo-

degeneration are related to incomplete emptying of the dilated failing ventricle, with a resultant intraventricular stasis of blood having a reduced oxygen content. It has been established that a narrow zone of the ventricular and intraventricular subendocardial myocardium is nourished from blood contained within the ventricular cavities themselves. When mural thrombi are not present, the subendocardial hydropic degeneration is limited to the narrow zone usually spared in myocardial infarction.³ As a result of the circulatory stasis, oxygenation and nutrition of the subendocardial tissue are inadequate. The inadequate oxygenation and nutrition become manifest anatomically by hydropic degeneration and by necrosis and fibrosis of the tissue in this region. Such a sequence of events often leads to the formation of mural thrombi and to thrombosis of the thebesian veins in the involved areas.

The question of the clinical and physiological significance of these related phenomena may be justifiably raised although not conclusively answered by the data given here. In the second case report, a clinical and pathologic study yielded no adequate explanation of the repeated bouts of cardiac decompensation. It seems conceivable that following an initial episode of failure, caused perhaps by beriberi or some obscure toxic myocarditis, the heart may have been left functionally impaired, due to the morphologic changes described in this report. The correlation between the degree of anatomic valvular or peripheral vascular handicap of the heart and the severity of clinical heart disease is often not close. It is suggested therefore that these changes caused by intraventricular circulatory stasis in heart failure may predispose the heart to further episodes of decompensation.

SUMMARY

The cardiac pathology of 10 cases of heart disease which were characterized clinically by signs of myocardial insufficiency, and anatomically by ventricular dilatation, is given. Four of the patients had hypertensive heart disease; one, rheumatic heart disease; two, coronary arteriosclerotic heart disease; one, hypertension with coronary arteriosclerotic heart disease; one, a possible toxic myocarditis; and one, possible beriberi heart disease. In all 10 cases there was a hydropic degeneration of the subendocardial myocardium of the dilated ventricle. In nine of the cases there was degeneration of the endocardium, either in the form of endocardial fibrosis or fibrinoid necrosis with or without leucocytic infiltration. In four of these cases there was, in addition to the endocardial and subendocardial degeneration, extensive mural thrombi and thromboses of the thebesian veins. The suggested pathogenesis of the afore-mentioned alterations is intraventricular circulatory stasis, with inadequate oxygenation and nutrition of the portion of tissue normally supplied by blood in the ventricular cavity.

CONCLUSIONS

1. Endocardial and subendocardial myocardial degeneration are common morphologic alterations in patients dying of congestive heart failure.
2. Following subendocardial degeneration, mural thrombi and thromboses of the thebesian veins may occur. The thromboses of the thebesian veins are

carditis, old or recent. All four chambers of the heart were lined by mural thrombi shading from red to gray. There was extensive endocardial fibrosis and subendocardial hydropic degeneration. The thebesian veins in these areas contained completely organized thrombi, making identification of the vessels difficult. No significant coronary arteriosclerosis was present. The heart valves were all normal. The etiology of the heart disease in this case is obscure. Similar cases have been ascribed, by Dock,¹ to beriberi. Smith and Furth² reported five cases in which there were cardiac hypertrophy and dilatation, and fibrosis of the endocardium and myocardium with mural thrombotic formation not attributable to arteriosclerosis, hypertension, or valvular heart disease. They raised the question as to whether the cardiac findings were associated with a deficient diet. In the case reported in this paper the patient was in comfortable economic circumstances during the latter part of his clinical course. At the onset of his illness he was in the Army, presumably eating at an Army mess.

TABULATED CASES

To determine the relative frequency of endocardial and subendocardial degeneration, mural thrombi, and thrombosis of the thebesian veins, eight autopsied cases of cardiac failure which were studied at necropsy were selected and the cardiac findings were tabulated. The criteria used in selecting these cases were clinical evidence of congestive failure and absence of anatomic evidence of myocardial infarction.

The etiology of the cardiac failure in the eight tabulated cases and the detailed case reports follow:

Hypertensive heart disease	4 cases
Rheumatic heart disease	1 case
Coronary arteriosclerotic heart disease	2 cases
Hypertension and coronary arteriosclerotic heart disease	1 case
Toxic myocardial disease	1 case
Beriberi (?)	1 case

Special stains indicated that the hydropic appearance is not related to glycogen deposition. In four of the cases fat stains showed the hydropic fibers to contain finely divided lipid.

DISCUSSION

It is to be noted that from an anatomic standpoint these 10 cases have in common the anatomic finding of cardiac dilatation and from a clinical standpoint evidence of ventricular failure. In all 10 hearts there was hydropic degeneration of the subendocardial myocardium of the dilated ventricle. In nine there was degeneration of the endocardium in the form of either fibrosis or fibrinoid necrosis. In four of these cases there were, in addition to the endocardial and subendocardial degeneration, extensive mural thrombi and thromboses of the thebesian veins. There were no instances of thromboses of the thebesian veins without mural thrombi or vice versa. The thromboses of the thebesian veins are undoubtedly secondary to the mural thrombus formation. It is suggested that the subendocardial fibrosis and subendocardial hydropic

Clinical Reports

VENTRICULAR FIBRILLATION

WITH SPECIAL REFERENCE TO THE MORGAGNI-ADAMS-STOKES SYNDROME;
REPORT OF AN UNUSUAL CASE

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IN 1769 Morgagni first described a case of cardiac syncope with convulsive manifestations. This report was followed by similar reports by Adams in 1827 and by Stokes in 1846. Since these early reports, the slowness of the pulse has been the factor emphasized by most observers.¹ In fact, most textbook descriptions limit the term Morgagni-Adams-Stokes syndrome to those cases of syncope accompanied by slowness of the pulse. The Criteria of the New York Heart Association defines the Adams-Stokes syndrome as "that condition in which there are attacks characterized by unconsciousness, often accompanied by muscle twitchings, and even general convulsions. 'These attacks occur in patients with auriculoventricular block when the ventricular diastole is sufficiently prolonged to result in a severe grade of cerebral ischemia.' The duration and severity of an attack depend upon the length of the ventricular diastole."² The term is not applied to syncope due to other causes. However, in spite of this definition and its general acceptance, we feel that the concept of Parkinson, Papp, and Evans³ is more accurate since the original observers had no electrocardiographic studies by which to determine the true cause of the bradycardia and the resultant syncope. Certainly another mechanism, which we shall discuss as a causal factor of the syncopal attack, occurs with sufficient frequency to warrant its inclusion in the definition of the Morgagni-Adams-Stokes syndrome.

As a matter of fact, Parkinson and his co-workers,³ in a careful review of the literature up to 1941, found that of 64 cases in which electrocardiographic studies were made during the unconsciousness of the Adams-Stokes attack, almost one-half of the attacks were due to ventricular fibrillation and tachycardia and not to ventricular standstill alone. In view of these data, it is no longer compatible with fact to state that only instances of auriculoventricular or ventricular standstill be included in this syndrome. We feel, therefore, that the definition proposed by Parkinson, Papp, and Evans is much

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secondary to the mural thrombi; the opposite is not true. These two findings are invariably associated.

3. These morphologic alterations can be explained on the basis of intra-ventricular circulatory stasis.

4. It is reasonable to expect that these morphologic changes further impair the function of the heart.

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prefibrillatory period was followed directly by ventricular standstill. This case serves to point out the facts that, although the three stages of Schwartz should be kept in mind, they are not absolute and that many cases do not conform to this classification, even though they are undisputed instances of Adams-Stokes disease. Moreover, the mere appearance of an arrhythmia prior to syncope does not necessarily mean that the syncope must be due to ventricular fibrillation, for it may also be caused by ventricular standstill alone.

In this brief discussion of the mechanism of ventricular fibrillation in Adams-Stokes disease, it will be of practical benefit to point out also the other conditions which may be instrumental in producing the syndrome. Cowan and Ritchie,⁸ in a review of 78 cases of complete heart block, found that only one-third showed the Adams-Stokes syndrome. Graybiel and White,⁹ in their report of 72 cases of complete heart block, showed that only 44 had bouts of Adams-Stokes disease. Therefore complete heart block is not the only factor essential to the production of the syndrome. Both Scherf,¹⁰ in the German literature, and Parkinson and his co-workers,³ in the English, divide the patients showing Adams-Stokes syndrome into three main groups. In the first group, the syncope is caused by ventricular tachycardia with resultant insufficient diastolic filling. The length of time before syncope will occur depends on the strength of the myocardium and the state of the arterioles at the time. In the second group, the symptoms are due to ventricular asystole which results from the failure of the ventricle to take over and establish its idioventricular rhythm. As we have previously mentioned, when this mechanism is active, it is difficult to determine by clinical method whether the asystole is of neurogenic or myogenic origin. In the third group, syncope is the result of a combination of ventricular tachycardia, with a subsequent period of ventricular asystole.

In most of the cases reported in the literature, the patients are among the older age group. This further emphasizes the fact that the state of the myocardium and the patency of the cerebral blood vessels play a definite and important role. As we have previously mentioned, the only recorded case in the younger age group is that of a 26-year-old man, reported by Borg and Johnson.⁷

We had the good fortune to observe a patient who suffered an attack of syncope produced by a combination of ventricular tachycardia, ventricular fibrillation, and ventricular standstill. We were able to record electrocardiographically the entire attack. Since only fifteen such cases are on record, this case has theoretical and clinical interest.

CASE REPORT

A. S., a 73-year-old white housewife, was admitted to the Newark Beth Israel Hospital, Dec. 11, 1943, following an attack of syncope. The past history was negative except that the patient had had two previous attacks of syncope. Five years before she had suffered her first attack when the door of a subway train closed upon her. Three years before our studies, the patient, who was an ardent horse race fan, suffered an attack of syncope as she was leaving the Belmont Race Track.

more applicable and should be generally accepted. They defined Stokes-Adams disease as "that condition which is seen in patients with heart block, who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these." It is important to bear in mind that in true Stokes-Adams disease, when there is ventricular standstill, the auricles continue to beat, whereas in other conditions of cardiac syncope there may be total cardiac asystole. Thus, this definition excludes cardiac syncope due to neurogenic or myogenic causes, such as vasovagal reflexes from stimulation of the carotid sinus, paroxysmal ventricular tachycardia complicating nodal bradycardia, and severe myocardial damage such as is seen in certain infections, all of which result in attacks of unconsciousness simulating Adams-Stokes disease. The absence of heart block and the episodic nature of the attacks readily distinguish them from the true Adams-Stokes syndrome.

Ventricular fibrillation, ventricular tachycardia, and ventricular standstill have usually been described in conjunction with the agonal phenomena of the dying heart.⁴ Only rarely have such arrhythmias been recorded in patients who have survived for any length of time. To date, only 28 such cases have been recorded, 13 of which showed ventricular tachycardia and ventricular fibrillation only, without cardiac standstill. The reason for such paucity of clinical material is obvious; ventricular fibrillation is usually fatal, so that a study of this arrhythmia in the living is extremely rare and therefore always worthy of careful observation and analysis. The mechanism for the production of ventricular fibrillation suggested by Wiggers⁵ is as follows: A premature systole appears during the vulnerable period of early diastole or late systole when certain elements of the cardiac syncytium have passed out of their refractory state. The impulse thus set up will weave its way through nonrefractory myocardial tissue to form a small wave front from which daughter excitation waves pass out over large portions of the myocardium. Then by the phenomenon of re-entry, smaller blocks of myocardium develop an independent excitation. The anoxia caused by incoordinated ventricular contractions causes failure of the coronary blood flow, which further slows conduction in the cardiac syncytium, decreasing fractionate contraction even more. This establishes the ventricular fibrillation.

Schwartz⁶ divided recurrent ventricular fibrillation into three stages. The first he designated as the prefibrillatory, the second as the fibrillatory, and the third as the postfibrillatory period. In the first stage there is an acceleration of the ventricular rate, with many extrasystoles of multifocal origin. The fibrillating stage shows a high rate of bizarre ventricular complexes appearing in irregular fashion. In the third stage there is a variable degree of ventricular standstill followed by ventricular tachycardia before the restoration of the basic ventricular rhythm. In this connection, it is worth mentioning that in 1937 Borg and Johnson⁷ reported a case of a 26-year-old man with syncope; they found that there was a stage of arrhythmia preceding unconsciousness, though no ventricular fibrillation occurred. In this patient the

Her present illness dates back to Dec. 11, 1944, when the patient was found unconscious, in the street, in front of the office of one of the authors. She was in a completely unconscious state. Her face was cyanotic and flushed, and the pulse and heart sounds were unobtainable. No localized neurological signs could be elicited on cursory examination.

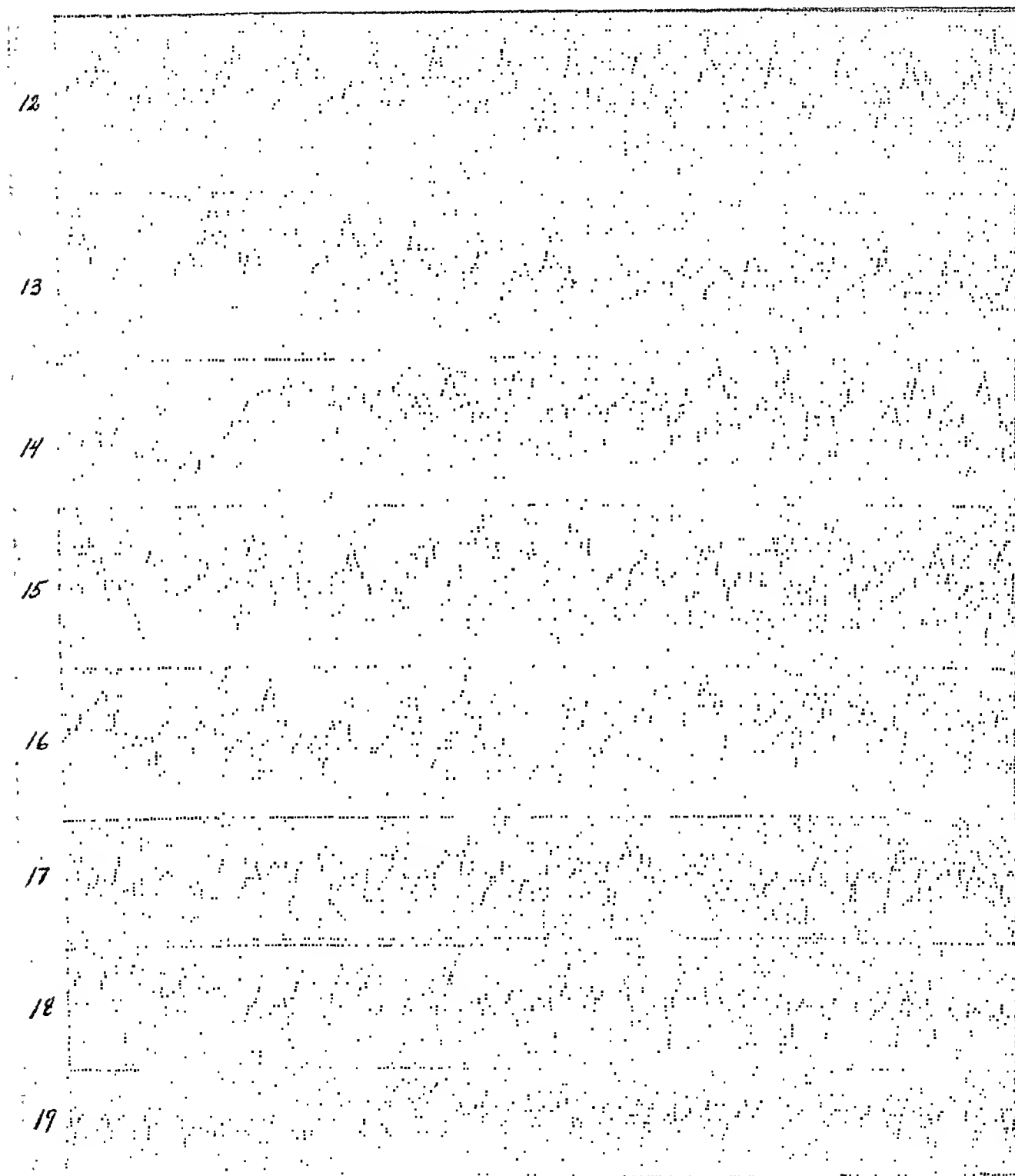


Fig. 1B.—(For legend see Fig. 1A.)

After several minutes, the patient vomited several times and developed clonic muscular twitchings involving both upper and lower extremities. During the ambulance ride to the hospital, she regained consciousness. Upon arrival at the hospital, her mind partially cleared, but she was thoroughly disoriented as to time and place and rambled vociferously.

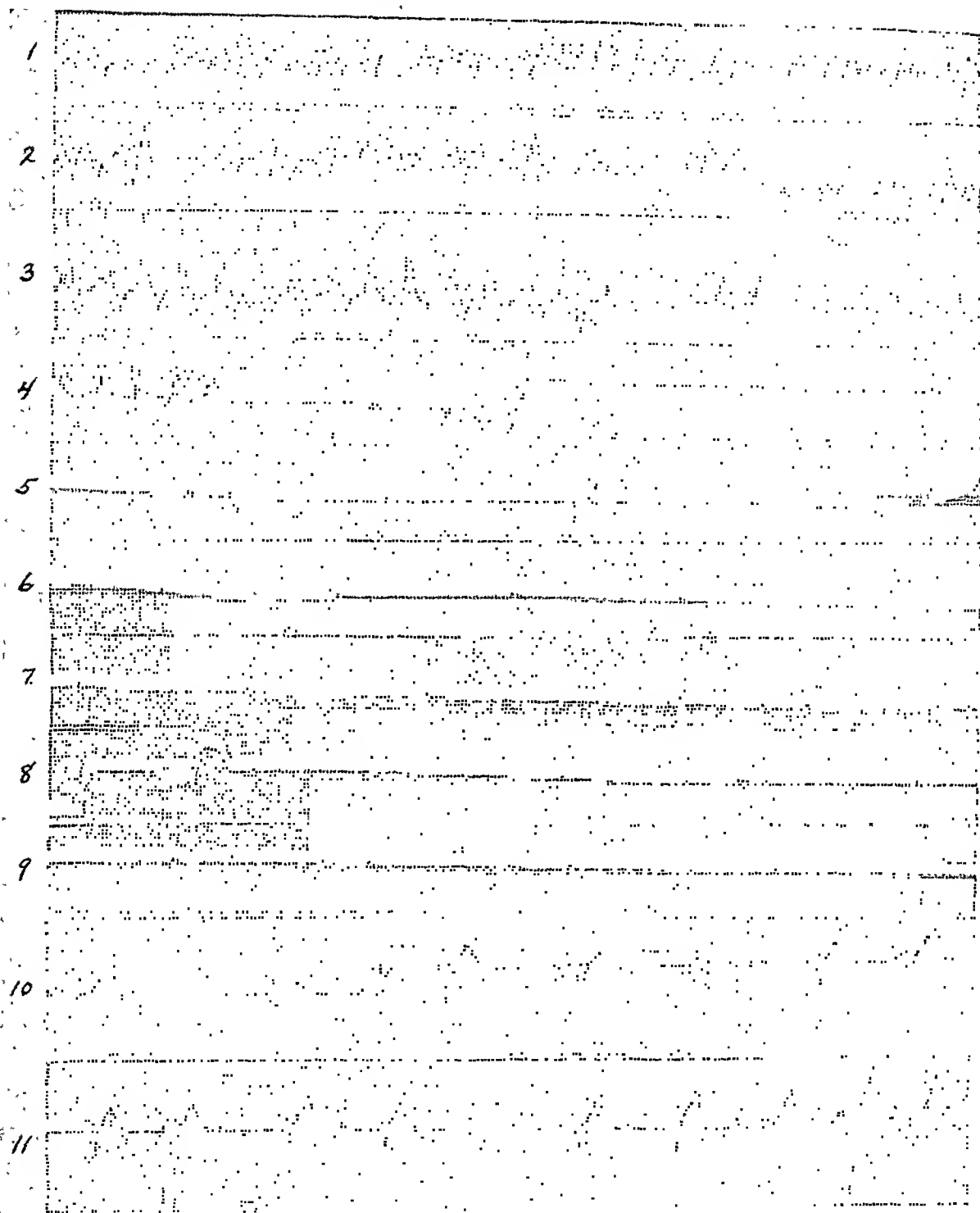


Fig. 1A.

Figs. 1A, 1B, 1C, and 1D.—This is a continuous tracing, taken entirely on Lead III, during the patient's period of unconsciousness. Since it was started a few moments after the patient developed syncope, the presyncopal period is not recorded.

There is a period of ventricular fibrillation (Strips 1 and 2), followed by a short period of ventricular tachycardia (Strip 3). Ventricular standstill of 60.8 seconds is then seen (Strips 4 to 9). The auricles continue to function during the entire ventricular standstill at the rate of 32 beats per minute. A few idioventricular beats then occur, followed by ventricular beats from various foci (Strips 10 and 11). A period of pseudobigeminy, as a result of bidirectional complexes, is then seen, followed by so-called "chaotic heart action," in which multiple ventricular foci produce idioventricular beats of varied contour (Strips 12 to 22). This arrhythmia continues until the basic complete heart block appears for a short time (Strip 23). Then ventricular tachycardia interspersed with heart block recurs (Strips 24 and 25). Finally, the heart block is re-established as the dominant rhythm (Fig. 1D).

Physical examination revealed that the patient looked her stated 73 years of age. She could lie flat in bed. She was pale, rather than cyanotic. The pupils were equal and reacted to light and accommodation. The external ocular muscles were normal, the fundi showed an increased silver wire effect with prominent A-V nicking, the discs were negative, and there were no hemorrhages or exudates. The examination of the nose and ears was negative. The mouth was moist and clean. The pharynx was negative; the tonsils were small and imbedded. The neck veins were not distended. There was no lymphadenopathy and no thyroid enlargement. The chest was clear. The point of maximum impulse was located in the fifth intercostal space outside of the midclavicular line. The heart sounds were of good quality; a third heart sound, heard between two normal beats, was interpreted as being due to auricular beats. A_2 was greater than P_2 . There was a loud, harsh, long systolic murmur at the apex, transmitted to the anterior axillary line; another systolic murmur, somewhat softer, was heard at the aortic area. The pulse rate and ventricular rate were 42 per minute. The blood pressure was 180/60. The liver, kidneys, and spleen were not felt; there was no tenderness nor rigidity, and no palpable masses in the abdomen. The examination of the extremities showed marked Heberden's nodes, but no cyanosis, edema or clubbing; peripheral sclerosis was present. On neurological examination, the deep reflexes were equal and active; no pathologic reflexes were elicited.

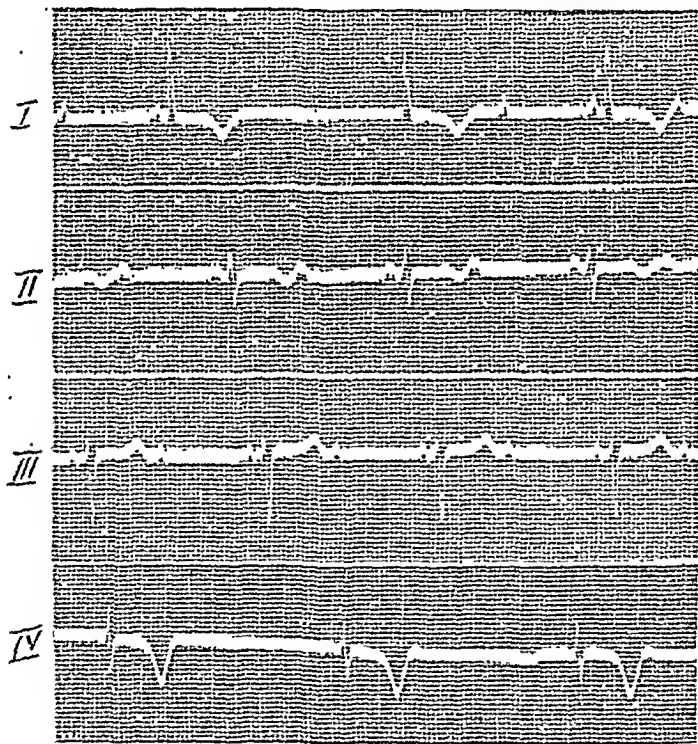


Fig. 2.—Tracing taken the day following, when the patient was apparently in her normal state. The rhythm is a two-to-one heart block with a nodal escape beat seen in Lead I. The abnormalities noted are inverted T waves in Leads I, II, and IV, with left axis deviation.

The clinical diagnosis was arteriosclerosis and hypertension, enlarged heart, mitral insufficiency, dilated aorta with complete A-V heart block, and Adams-Stokes syndrome.

The patient was placed on phenobarbital, $\frac{1}{2}$ grain four times daily, and papaverine, $1\frac{1}{2}$ grains three times daily. She remained much quieter and had no convulsive or syncopeal episodes.

On Dec. 12, 1943, she was taken to the electrocardiographic department. When the electrodes were applied, she suddenly turned a cadaveric white, the respiration ceased, the heart sounds became inaudible and the pulse imperceptible. The patient made a few gasping respiratory movements, and the pupils dilated. During this time, sphincter control ceased and she became incontinent of urine and feces. A continuous tracing of the events in the heart, during this whole episode will be found in the accompanying electrocardio-

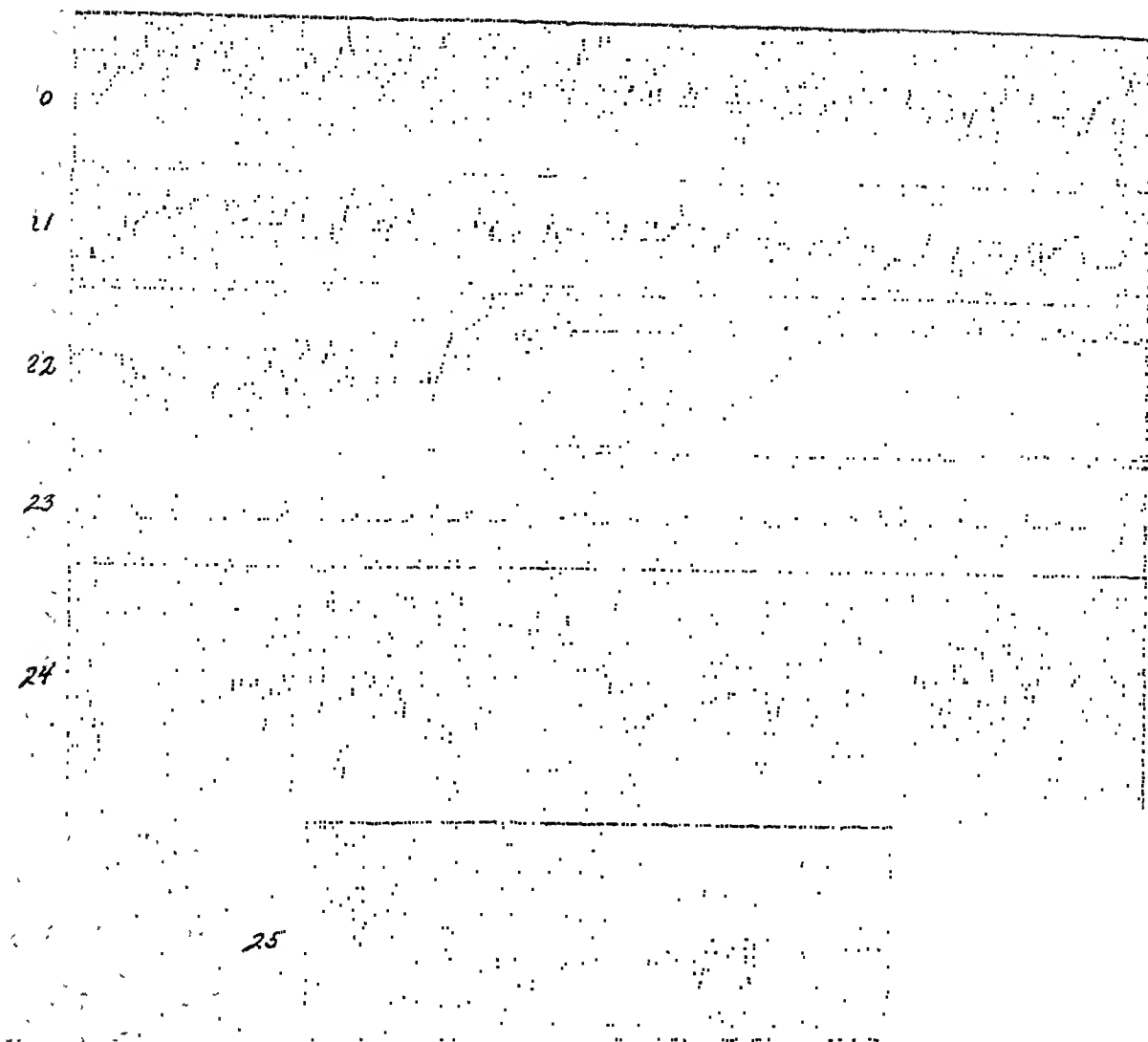


Fig. 1C.—(For legend see Fig. 1A.)

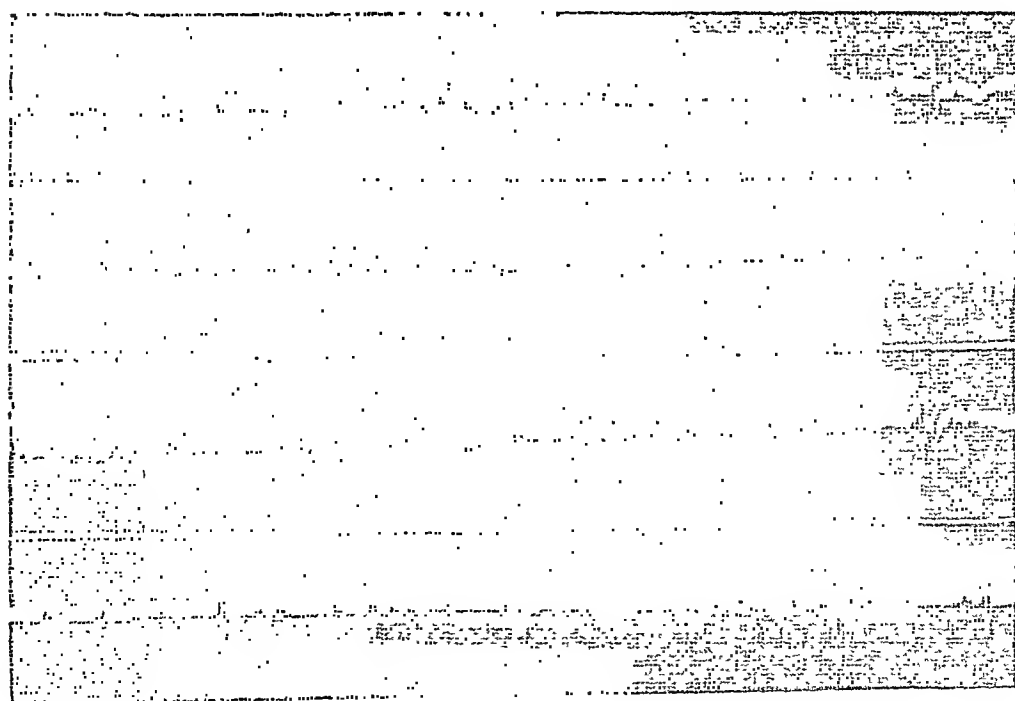


Fig. 1D.—(For legend see Fig. 1A.)

attack. Our case is unique in that the patient is still active eighteen months after the recorded seizure and probably five or six years following the initial attack.

It may be pertinent to discuss the various forms of treatment suggested for this condition. Many years ago barium chloride was recommended as the drug most likely to prevent Adams-Stokes syncope. However, Parsonnet and Hyman,¹³ in a carefully controlled experimental study concluded that this drug was of no value. The use of adrenalin or ephedrine has been proposed because these drugs are such powerful cardiac stimulants; unfortunately, their true value in the therapy of this condition is not very clear. There is some evidence to show that in chloroform anesthesia the administration of adrenalin may, in itself, induce ventricular fibrillation.¹⁴ Ephedrine, too, because of its irritating effect on the myocardium, may be a dangerous drug in spite of the fact that theoretically it should prevent ventricular standstill. Quinidine sulfate has been used prophylactically in an attempt to prevent some of the arrhythmias, especially the extrasystolic ones, and thus forestall ventricular fibrillation. The experiments on dogs by Smith and his collaborators¹² are especially suggestive. However, quinidine, in excess, produces ventricular fibrillation in the experimental animal. More recently, Katz¹⁵ suggested the use of papaverine in large doses. Experimentally, at least, this drug has been found effective in both stopping and preventing ventricular fibrillation. From the previous consideration, it is evident that of the drugs suggested, the ideal one for the treatment of Adams-Stokes disease, or the component arrhythmias that produce it, has not yet been found. Until a better drug is found, therefore, papaverine in large doses, or perhaps quinidine, is the remedy of choice.

The report of this case helps to summarize the known facts on the Morgagni-Adams-Stokes syndrome, as well as on ventricular fibrillation. The patient was a woman, 73 years of age, when first seen. However, the condition must have been present for at least five years, in view of a clear-cut history of syncopal attacks five and three years prior to hospital admission. The observed attack did not demonstrate very clearly the three stages suggested by Schwartz; we were unable to record the so-called prefibrillatory period in our tracings. However, this stage may have been of such short duration that it was not observed before the onset of syncope. On the other hand, that the syncopal period followed the rather typical course pointed out by Parkinson is clearly demonstrated in the tracings. Ventricular fibrillation with a rapid rate was followed by a period of rapid ventricular tachycardia which was followed by another short period of ventricular fibrillation and, finally, by ventricular asystole. The auricles continued to beat during the entire period of ventricular asystole which, in this particular seizure, lasted for one full minute. The longest period of asystole thus far recorded is seventy-nine seconds.¹⁶ In our case, the asystolic period was followed by ventricular tachycardia with idioventricular beats and multifocal extrasystoles. Finally, a run of ectopic beats with bidirectional complexes appeared, and the heart rate slowed enough so that, when consciousness returned, the rhythm reverted to the heart block, which was originally present.

grams (Fig. 1). Soon the face of the patient became suffused and cyanotic, there were some deep, sporadic respiratory movements, and the patient gradually returned to consciousness. During the ensuing three days the patient had several further seizures, each following the same general pattern. Fig. 2 illustrates the rhythm on the third day when the pulse was 40 per minute. After these episodes, she remained free from attacks, and her mind returned to normal. On the seventh day she refused to stay in bed and insisted on going home. She was discharged at her own risk.

Following these episodes, the patient has consistently refused medical care of any kind. She is perfectly rational, does her own housework, and will not permit further electrocardiographic studies to be made. Eighteen months have now passed since the first tracing was taken, and the patient has returned to full activity. Recently she was observed lifting bundles of paper averaging more than 20 pounds each.

DISCUSSION

A number of investigators have recorded cases of ventricular fibrillation, both in Adams-Stokes disease and in the dying heart. These reports emphasize the fact that ventricular fibrillation is rarely seen in the Adams-Stokes syndrome, unless the basic rhythm is some degree of heart block. Furthermore, the time when ventricular fibrillation is most apt to occur, is during the transition from partial to complete A-V heart block. However, this is not an inflexible rule, since cases have been recorded in which a patient with partial heart block has developed ventricular fibrillation without ever having reached a stage of complete auriculoventricular dissociation.

Instances of Adams-Stokes disease, which occurred during acute myocardial infarction following coronary occlusion, have been reported. Beckwith¹¹ recorded three such cases which demonstrated different underlying mechanisms. Complete heart block was present in one case and paroxysmal ventricular tachycardia in another; both conditions were present in the third. In none of the three patients were the syncopal attacks registered electrocardiographically.

Experimental ventricular fibrillation may be induced by ligation of one of the coronary arteries; it is therefore felt that this arrhythmia may be responsible for sudden death in acute myocardial infarction in the human subject. It is believed that afferent impulses from the infarcted area give rise to reflex coronary spasm by way of the vagi. This results in myocardial anoxia which may initiate the premature contractions that lead to fibrillation. It is interesting that Smith, McEachern, and Hall¹² found that the mortality rate from sudden occlusion of the left coronary artery in normal dogs could be reduced from 75 per cent to 50 per cent by the administration of quinidine. Death in these animals was usually due to ventricular tachycardia, followed by ventricular fibrillation. Quinidine seemed to prevent much of the pain of the occlusion. It is interesting to note that when quinidine was used instances of ventricular tachycardia and extrasystoles were more frequent, though there were fewer cases of ventricular fibrillation.

The prognosis, at best, is uncertain. Such patients usually have had advanced arteriosclerotic heart disease with marked coronary arteriosclerosis and myocardial fibrosis, and rarely survive more than a few months after an

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ADDENDUM

April 15, 1946: This patient is still alive and able to carry on her daily routine as a housewife, two years and four months after the recorded attack. She refuses, however, to permit further study.

In the treatment of the condition, the only drug used was papaverine in large doses. It is difficult to say whether or not this contributed to our patient's recovery, since she recovered from her previous attacks without medication. During the past eighteen months she has taken no medication and apparently has had no further seizures.

It is important from a prognostic point of view to discuss the question of longevity in such cases. In the series of 56 patients reported by Parkinson and his co-workers, there were 15 with ventricular standstill alone. Five of these died during the attack and seven lived and were free from seizures for from three months to four and one-half years after the onset of Adams-Stokes disease. The remaining three of the series died of noncardiac causes. Of 20 cases similar to our own, 15 patients died during the attack and five died within a year after discharge. Only four of this group were alive after three to ten months.

Based upon the previous data, the prognosis in cases with very rapid ventricular tachycardia and fibrillation is immediately grave. However, if the patient recovers from the initial syncopal seizure, the life expectancy is about one year. Our patient has survived for 18 months after the one attack which was graphically recorded, and has probably lived now for six years since her first syncopal seizure which we assume to have been similar in character to the attack which we recorded.

SUMMARY

1. We have discussed the definition of the condition known as Adams-Stokes disease, or the Morgagni-Adams-Stokes syndrome. Based upon the review of the literature, we feel that the Adams-Stokes syndrome should include not only cases of ventricular standstill with loss of consciousness, but also those of syncope due to ventricular tachycardia or ventricular fibrillation.

2. An instance of this condition is reported which is unusual in that the patient lived six years, which is much longer than most patients live after the onset of syncope.

3. The varied methods of treatment are briefly summarized and found to be inadequate. At the present time, quinidine and papaverine seem to be the drugs of choice.

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no neck rigidity and no enlargement of the cervical nodes or of the thyroid. The lungs were essentially normal. The heart was not enlarged; the rhythm was regular and the rate was 74 beats per minute. The sounds were of good quality and no murmurs nor friction rub were heard. The blood pressure was 130/78. The abdomen was normal. There was incontinence of feces. The musculoskeletal system was essentially normal, and all reflexes were present and equal, bilaterally. There was no impairment of any of the cranial nerves.

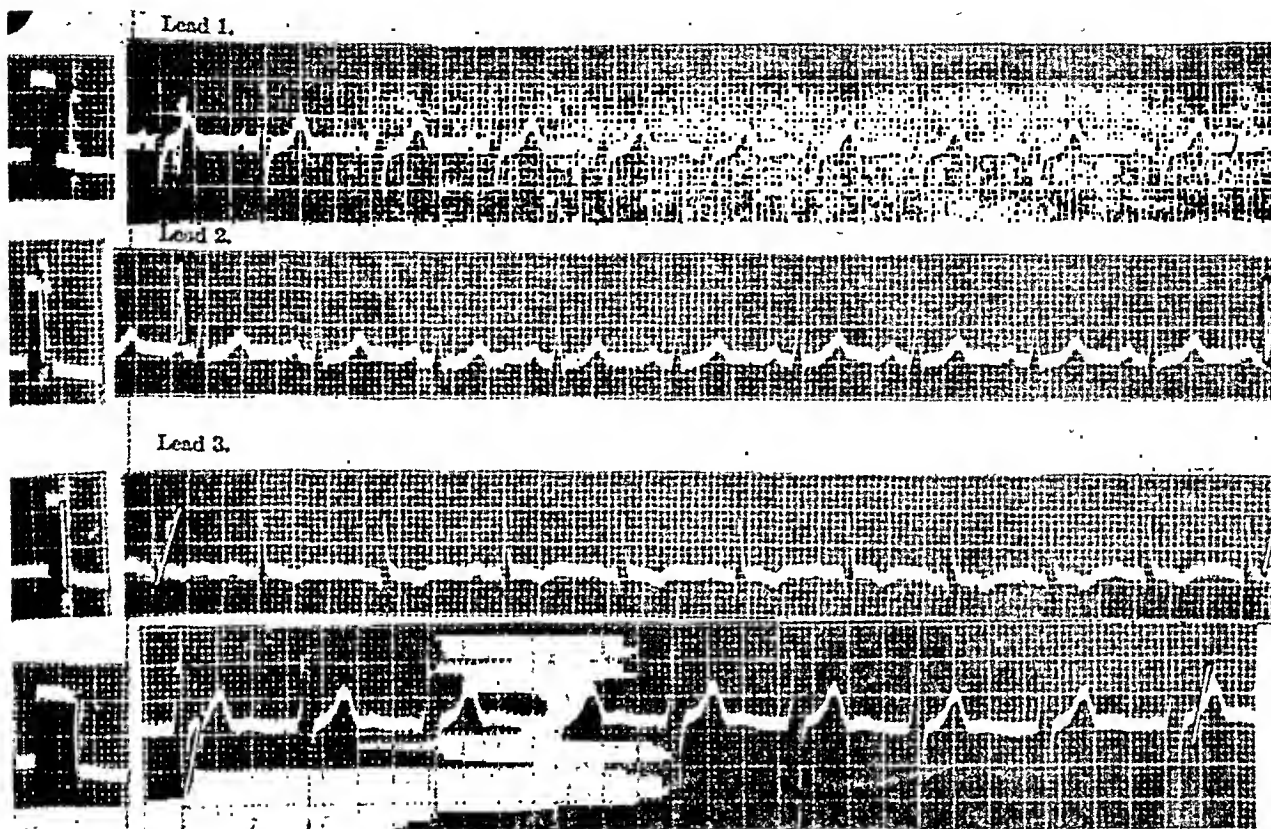


Fig. 1.—Electrocardiogram taken four hours after first episode of syncope.

Course.—Within two hours after the acute episode, the patient was feeling much better but still complained of a slight pain in the chest, substernally. The temperature, pulse, and respirations were all normal. The skin was warm, there was no evidence of cyanosis, and the patient was well oriented and rational. An electrocardiogram (Fig. 1) taken at this time revealed a regular sinus rhythm, a rate of 88 beats per minute, a deep S_1 , and inversion of T_1 . The electrocardiogram was interpreted as being within normal limits. The patient was kept on absolute bed rest and given phenobarbital, $11\frac{1}{2}$ grains, at bedtime. On Feb. 8, 1945, the day following the acute episode, he complained of a persistent, mild substernal pain. This symptom recurred on several occasions during the following weeks. It was noted at this time that the patient had a rather large conjunctival hemorrhage in the right eye. The external ocular muscles, vision, and fundi were found to be normal. The blood pressure was 146/78. All reflexes were present and equal. There was no evidence of any neurological pathology and no derangement of the cranial nerves. The patient remained on complete bed rest from Feb. 7, 1945, until Feb. 20, 1945. During this period the temperature remained consistently normal. The white blood count, taken on Feb. 8, 1945, revealed 8,200 white blood cells, with 52 per cent polymorphonuclears, 44 per cent lymphocytes, 2 eosinophiles, and 2 monocytes. The sedimentation rate was 7 mm. in one hour. On Feb. 13, 1945, the test revealed 7,400 white blood cells, with 50 per cent polymorphonuclears, 48 per cent lymphocytes, and two eosinophiles. The sedimentation rate was 6 mm. in one hour. The Kahn test for syphilis was negative. The electrocardiogram taken Feb. 12, 1945 (Fig. 2), was interpreted as being within normal limits. In the absence of physical or laboratory findings of myocardial injury, the patient was allowed to

FATAL CORONARY FAILURE WITHOUT INFARCTION: REPORT OF A CASE

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FOR many years it has been taught that coronary artery disease primarily affects patients in middle life, but that it may occur infrequently in younger people. It has become apparent, however, that the incidence of coronary artery disease in young people is greater than is generally realized. It is possible that in many cases of coronary artery disease in young people where certain significant symptoms are present, the physician may be misguided in his diagnosis or may be lulled into a false sense of security solely because of the youth of the patient. In many cases severe disability or even fatality may result.

REPORT OF CASE

History.—A 25-year-old white man was admitted to the Station Hospital at 10:45 A.M., on Feb. 7, 1945, in a semicomatose state. He was disoriented, cyanotic, and apparently in moderate shock. Approximately two hours after admission, when he was able to speak, he stated that he was well until one-half hour before admission, when he felt a pain around his heart, associated with some shortness of breath. These symptoms became progressively more severe, until he felt that he had to lie down. The last thing he remembers was stretching out on the ground outside the building in which he was working. Within a few minutes he was found, unconscious, by several of his fellow workers. He was bleeding from the nose and showed marked blueness of the hands and face. His pulse was said to be imperceptible. The breathing was described as very shallow, quickly becoming very irregular and weak. The blueness of the face and hands increased. After the administration of artificial respiration breathing improved considerably and the patient was brought to the hospital.

The history revealed that the patient had been a mechanic in civilian life, and was inducted into the Service in February, 1942. He smoked cigarettes moderately, drank a large amount of beer, and occasionally went on an alcoholic bout. He did not take any drugs. His father, mother, and one sister were living and well. An uncle on the paternal side had died of a heart attack at the age of 40 years. There was no other history of chronic or familial disease. He had had the usual childhood diseases, but no other illnesses except infrequent upper respiratory infections. He denied any venereal disease. He also stated that beginning approximately one month prior to this episode of fainting he noticed pain in the chest, localized under the breastbone, which occurred only following or during exertion, such as walking, physical training, or heavy lifting. He described the pain as a cramping sensation similar to muscle cramps. There was no radiation and the pain was definitely relieved by rest. He could not recall experiencing any attacks of pain while at rest. Although for two weeks prior to admission to the hospital, he was unable to keep up with his physical training periods because of the quick onset of this cramping sensation, he did not seek medical advice. He also stated that he had felt vague pains through his arms and legs during the month preceding admission. These pains were not related to the chest pain or to activity.

Physical Examination.—On admission the patient was disoriented, confused, and very anxious. He was stocky and heavyset. His height was 71 inches, and his weight was 180 pounds. His skin was cold and clammy; there was moderate cyanosis of the lips, face, and nail beds. The pupils were widely dilated and reacted sluggishly to light. There was evidence of fresh bleeding from the nose. The mouth and throat were normal. There was

DISCUSSION

This report concerns a 25-year-old white man whose history indicated that he had had angina pectoris for approximately four weeks, and then developed a sudden episode of syncope, from which he recovered quickly. The physical findings were essentially normal. After this acute episode he continued to have angina pectoris at rest (decubitus) for another four weeks and died suddenly one morning while in bed. French and Dock¹ state that more than 100 fatal cases of coronary arterial disease occurring in young soldiers between the ages of 20 and 36 years have been reported since the beginning of the war. In their excellent survey covering 80 such cases, they concluded that the basis of the coronary artery disease in all cases was arteriosclerosis. There was no predilection for any race or national origin; presumably the most striking predisposing factor was overweight, which was present in 91 per cent of the subjects. Our patient showed definite arteriosclerotic disease which involved both coronary arteries and also the ascending arch of the aorta. He was approximately 20 pounds overweight. Another interesting finding reported by French and Dock¹ in their series of 80 fatal cases was that recent myocardial infarction was demonstrated in only 15 of these cases. Fibrous myocardial scars with or without fresh necrosis were found in 39 cases. As a result of these findings, they postulated that coronary arteriosclerosis, or coronary occlusion without myocardial infarction, is the cause of death in younger men more frequently than in older patients. The post-mortem examination of our patient showed no evidence either grossly or microscopically of myocardial scars or recent infarction. It is very likely that, rather than true myocardial infarction, in a significant number of cases of coronary artery disease, myocardial ischemia, resulting in an abnormal cardiac rhythm, probably ventricular fibrillation, is the mechanism causing death.

The pathologic findings in our case admirably fit the concepts and conclusions promulgated by Blumgart and his co-workers.² They found that complete coronary occlusion, or considerable narrowing of one or more coronary arteries, may exist with no evidence of myocardial infarction. This could only be true if the occlusion proceeded slowly, allowing sufficient time to elapse for the formation of an adequate collateral coronary circulation. They also showed that 47 patients suffering primarily from angina pectoris, without evidence of valvular disease or arterial hypertension, had old complete occlusion of at least one major coronary artery at post-mortem examination. In our case, the history of true angina pectoris four weeks prior to the first episode of syncope strongly suggests a slowly progressing occlusion of the coronary artery.

It is of interest to speculate about the episode of syncope which brought the patient to the hospital and was followed by a five-week period of angina pectoris at rest. It is probable that the coronary occlusion resulted in a high degree of coronary insufficiency, but not in enough coronary insufficiency to produce a gross myocardial infarction. Myocardial ischemia resulting from the high degree of coronary insufficiency may very well have brought on an abnormal cardiac rhythm resulting in syncope and finally in death. White

increase his activity gradually, and to get out of bed on Feb. 21, 1945. On Feb. 25, 1945, he was given a two-hour pass to visit his barracks. He returned within a short time, stating that he had had to stop and rest three times in a distance of approximately two blocks because of precordial pain. The patient was again put on bed rest. At 7 A.M., on March 4, while still in bed, he complained of severe substernal pain, and in a few minutes went into acute circulatory collapse. He was given oxygen and $\frac{1}{4}$ grain of morphine, intravenously, but did not improve. He developed a gallop rhythm and expired thirty minutes after the onset of the precordial pain.

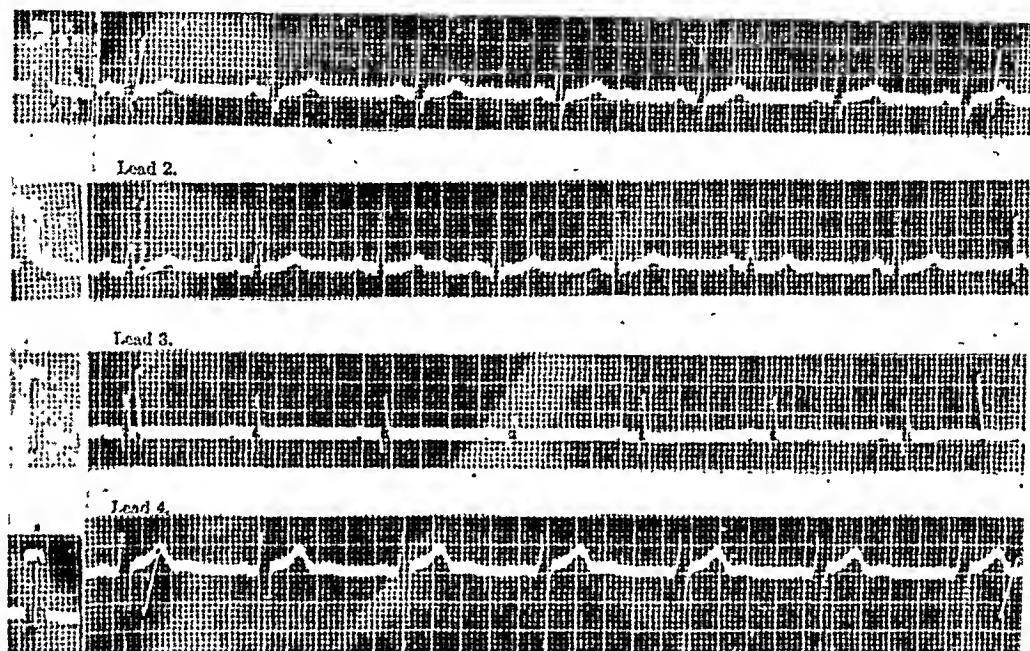


Fig. 2.—Electrocardiogram taken Feb. 12, 1945.

Necropsy.—Post-mortem examination revealed that the abnormal findings were confined entirely to the heart and aorta. A considerable fatty layer over the pericardial sac was cut through and the heart was exposed. There was a normal amount of clear yellowish fluid within the pericardial sac. The heart appeared to be of normal size, and weighed 380 grams. The right ventricle was relaxed and flabby; the left ventricle was firm and moderately contracted. The epicardium was smooth. The relationship between the musculature of the right and left ventricles was normal. Upon opening the heart several small clots which were not adherent to the endocardium were observed in the left ventricular chamber. The endocardium throughout both ventricles appeared smooth and glistening. The papillary muscles were normal. There was no evidence of old or recent myocardial scar formations. All the valves were found to be smooth and free. In the first portion of the ascending aorta a moderate amount of soft, atheromatous plaque formation was present on the wall of the vessel for a distance of approximately 2 inches above the valve. These plaques extended into the mouth of the left coronary artery. On opening the left coronary artery, an organized yellowish white thrombus was found, firmly adherent to the wall and extending from the mouth downward for a distance of approximately $1\frac{1}{2}$ inches. On peeling away this thrombus, considerable arteriosclerotic changes were observed in the endothelial lining of the coronary artery. It was impossible to pass a very fine probe into the artery because of the thrombus. The right coronary artery was patent and free throughout, allowing free passage of the probe, but, when the artery was opened there were observed, for a distance of approximately 2 inches from its mouth, scattered small areas of endothelial arteriosclerotic changes. Microscopic examination revealed no evidence of myocardial damage, either old or recent.

THE WOLFF-PARKINSON-WHITE SYNDROME IN ASSOCIATION
WITH CONGENITAL HEART DISEASE:
COARCTATION OF THE AORTA

REPORT OF A CASE

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ELECTROCARDIOGRAPHIC evidence of a short P-R interval and bundle branch block has been reported in the literature since 1915.¹ In recent years, this syndrome has been recognized and reported more and more frequently. Doubtless, numerous cases have never been reported. Wolff, Parkinson, and White² concluded that this syndrome consisted of functional bundle branch block and an abnormally short P-R interval occurring with paroxysms of tachycardia in otherwise healthy people. Hunter, Papp, and Parkinson³ reported 19 cases of their own and reviewed the 90 previously reported cases. They found that 18 of these patients and three of their own had cardiac disease which was considered incidental. The heart disease reported in association with this syndrome may be classified under the following etiological headings: rheumatic (mitral and aortic disease), syphilitic, hypertensive, arteriosclerotic (coronary), and thyrotoxic. Coexisting congenital heart disease has apparently not been reported.

Mention has been made as to the age at which this syndrome of short P-R interval with bundle branch block has occurred. The youngest patient on record in whom the syndrome occurred was a boy, 4½ years old. This case was reported by Hamburger⁴ in 1929.

This report includes the following unusual features: (1) The patient whose case history is recorded is apparently the youngest patient in whom the Wolff-Parkinson-White syndrome has been reported. (2) It seems likely that this is the first instance in which coexisting congenital heart disease has been recorded.

CASE REPORT

The patient was a white male child born on May 8, 1942. The family history yielded no evidence of cardiovascular disease. The child was delivered normally at term and weighed 7 pounds, 8 ounces. Nothing abnormal was noticed in the nursery at the hospital during the first ten days of his life. When the child was 4 weeks old, he developed an acute upper respiratory infection and was referred to a pediatrician for care. Examination at that time revealed a heart murmur. A roentgenogram of the chest was taken, and the mother was told that the child had an enlarged heart which was due to a congenital heart defect. The child made an uneventful recovery from the respiratory infection. On Aug. 14, 1942, another roentgenogram of the chest (Fig. 1) showed marked cardiac enlargement.

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and his associates,³ in their study of 497 cases of angina pectoris, reported that in 47 cases the average duration of life after the onset of angina at rest was 2.8 years. They wrote: "Coronary heart disease, whether shown by the angina pectoris of temporary coronary insufficiency or by myocardial infarction with subsequent scarring, is actually . . . , in the majority of cases, an acute or subacute rather than a chronic disease. This conception . . . is a vital one, of tremendous significance both in prognosis and treatment. . . . The natural tendency of the heart to establish an adequate collateral coronary circulation is the answer."

The electrocardiograms deserve brief mention. The first, taken four hours after the syncopal attack, at a time when the patient seemed to be completely recovered clinically except for mild residual, precordial pain, showed only a deep S_1 and an inverted T_3 . There was no evidence of RS-T depressions or of inversions of the T wave in more than one lead, as would be expected in a diagnosis of coronary insufficiency. The second electrocardiogram, taken five days later, showed a small diphasic T_3 and a decrease in the amplitude of S_1 from 5 mm. in the first electrocardiogram to 2 mm. in the second. We do not feel that these changes warrant an electrocardiographic diagnosis of coronary insufficiency. Stewart and Manning,⁴ in a detailed analysis of electrocardiograms taken on 500 members of the R. C. A. F. Air Crew, state that in 432 an S_1 with a mean amplitude of 2.8 mm. was present, and that in 140 of the cases there was a negative or diphasic T_3 . It is unfortunate that our instrument was out of order when we wished to have the patient undergo an exercise test. It is quite possible that an electrocardiogram taken immediately after exercise would have shown evidence of the coronary insufficiency.

SUMMARY

1. Coronary artery disease probably occurs more frequently in young persons than is generally supposed.
2. Both clinical and electrocardiographic findings may be normal.
3. The onset of angina pectoris of effort is the most important single prodromal symptom and should be given careful consideration.
4. A youthful age should not lull the physician into a false sense of security.
5. With the onset of angina pectoris the patient should be considered as acutely or subacutely ill, and so treated as to allow the heart to establish an adequate collateral circulation.

Grateful acknowledgment is made to the Army Museum of Pathology, Washington, D. C., for their pathologic studies on the heart in the case reported.

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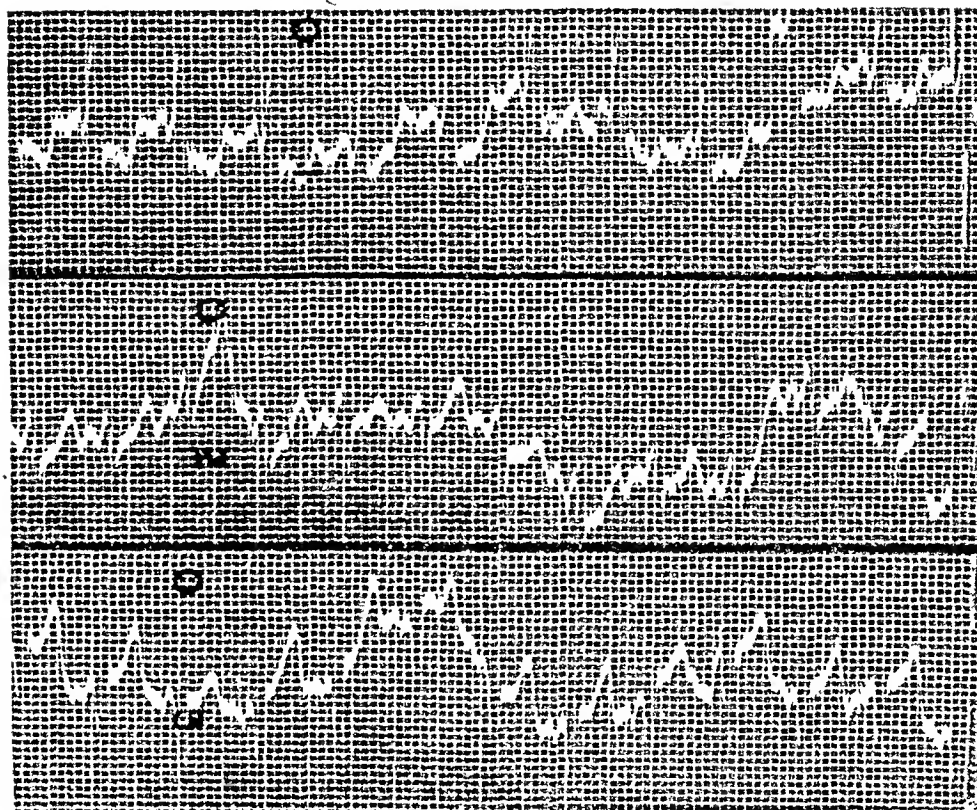


Fig. 2.—Aug. 23, 1942; see text for details.

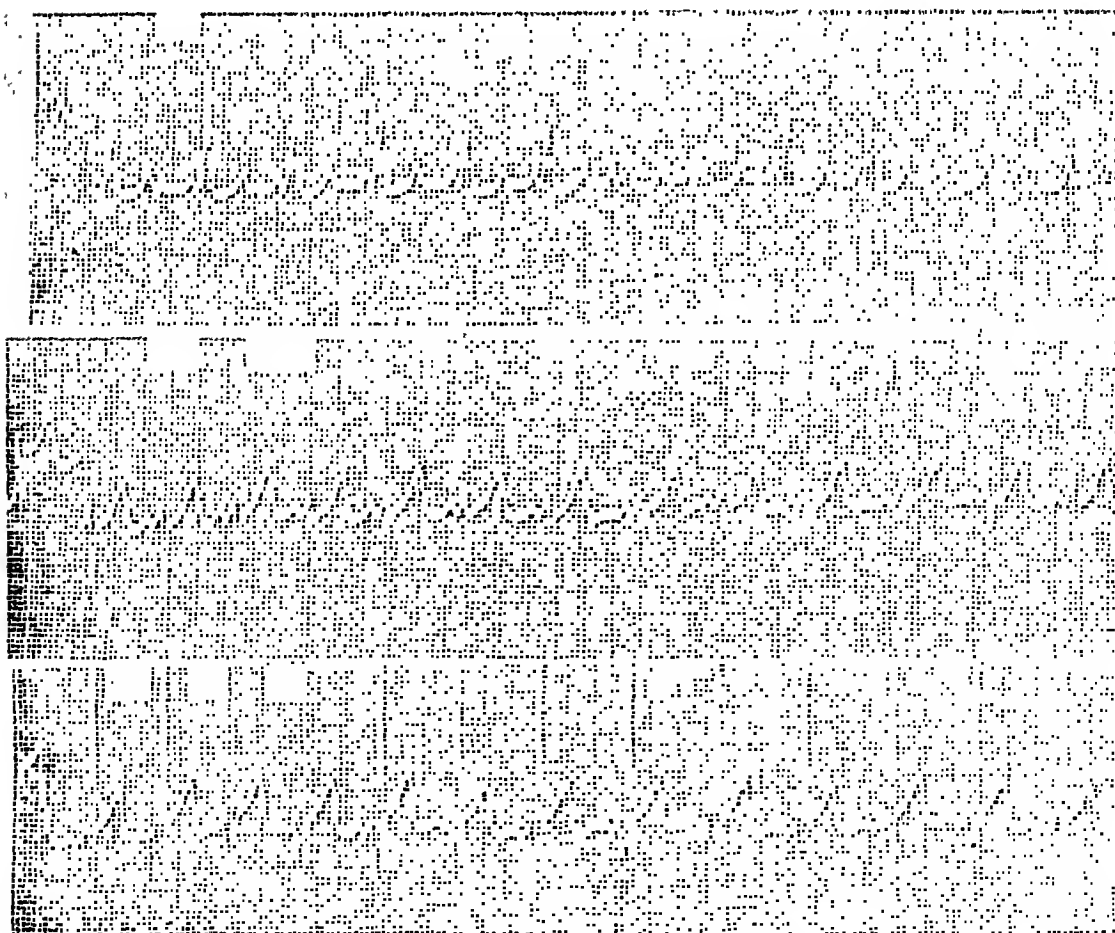


Fig. 3.—Oct. 4, 1944; the Wolff-Parkinson-White syndrome.

The child remained perfectly well until Aug. 22, 1942, when, at the age of 14 weeks, he had a spell in which he "became pale and acted as if he were in a half-faint; his heart was pounding and he was blue around the mouth." Hospitalization was recommended, and on admission at 6 P.M. the child was noted to be dyspneic, pale, slightly cyanotic, and "covered with a cold sweat." The apex beat was regular but very rapid and uncountable. There was a loud systolic murmur at the second intercostal space parasternally. There was also a systolic murmur at the apex, not transmitted. The blood pressure was 98/82 in the right arm and 110/84 in the left arm. The liver was $1\frac{1}{2}$ fingerbreadths below the ninth costal cartilage and was soft. There was no edema. At 8:30 P.M. the child looked better. His color was good, and there was no dyspnea. The heart rate was 147 per minute. There was a moderate blowing systolic murmur at the pulmonic area and a slight systolic murmur at the apex. The heart size was described as "huge." The following diagnosis was made: (1) paroxysmal tachycardia, and (2) probable congenital heart disease.



Fig. 1.—Routine roentgenogram of the chest, Aug. 14, 1942. Note the marked cardiac enlargement.

On Aug. 23, 1942, an electrocardiogram taken after the subsidence of rapid heart action was interpreted as "showing resemblance to the electrocardiogram found in adults with coronary artery disease during anginal pain. There was left axis deviation, sinus tachycardia, and S-T-segment and T-wave abnormalities resembling coronary insufficiency" (Fig. 2). The possibility of a coronary anomaly was considered. Attention was called to the fact that the cardiac enlargement, and S-T-segment, and T-wave abnormalities could possibly be the effects of the tachycardia. The urine was negative. The blood count disclosed a hemoglobin of 73 per cent; erythrocytes, 4,100,000; leucocytes, 12,550, of which 41 per cent were neutrophils, 49 per cent were lymphocytes, 8 per cent were monocytes, and 2 per cent were eosinophiles. A repeat electrocardiogram on Aug. 24, 1942, was exactly the same as the one taken the previous day. There were no further attacks of tachycardia; the child improved and was permitted to go home after two days of hospitalization.

From that time until April 25, 1945, the child was in good health, with the exception of "short attacks of rapid heart beat," which were noted by the mother, a former student nurse. She stated that these attacks seemed to terminate spontaneously. On Oct. 4, 1944, the child was brought into the office for a routine physical examination. An electrocardiogram taken at this time showed the characteristic tracing of the Wolff-Parkinson-White syndrome (Fig. 3). On Dec. 6, 1944, a routine electrocardiogram showed a normal P-R interval and a normal duration of the QRS complex. There were, however, S-T-segment and T-wave abnormalities (Fig. 4, *A*). On April 17, 1945, the child became pale and dyspneic and was brought into the office by his mother, who said that she was certain

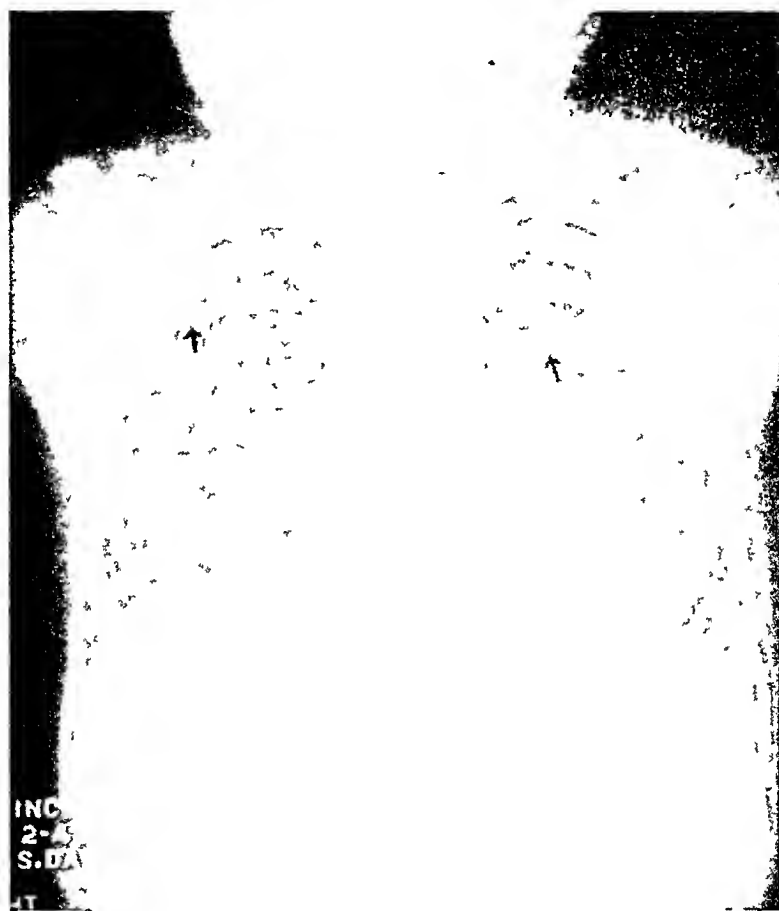
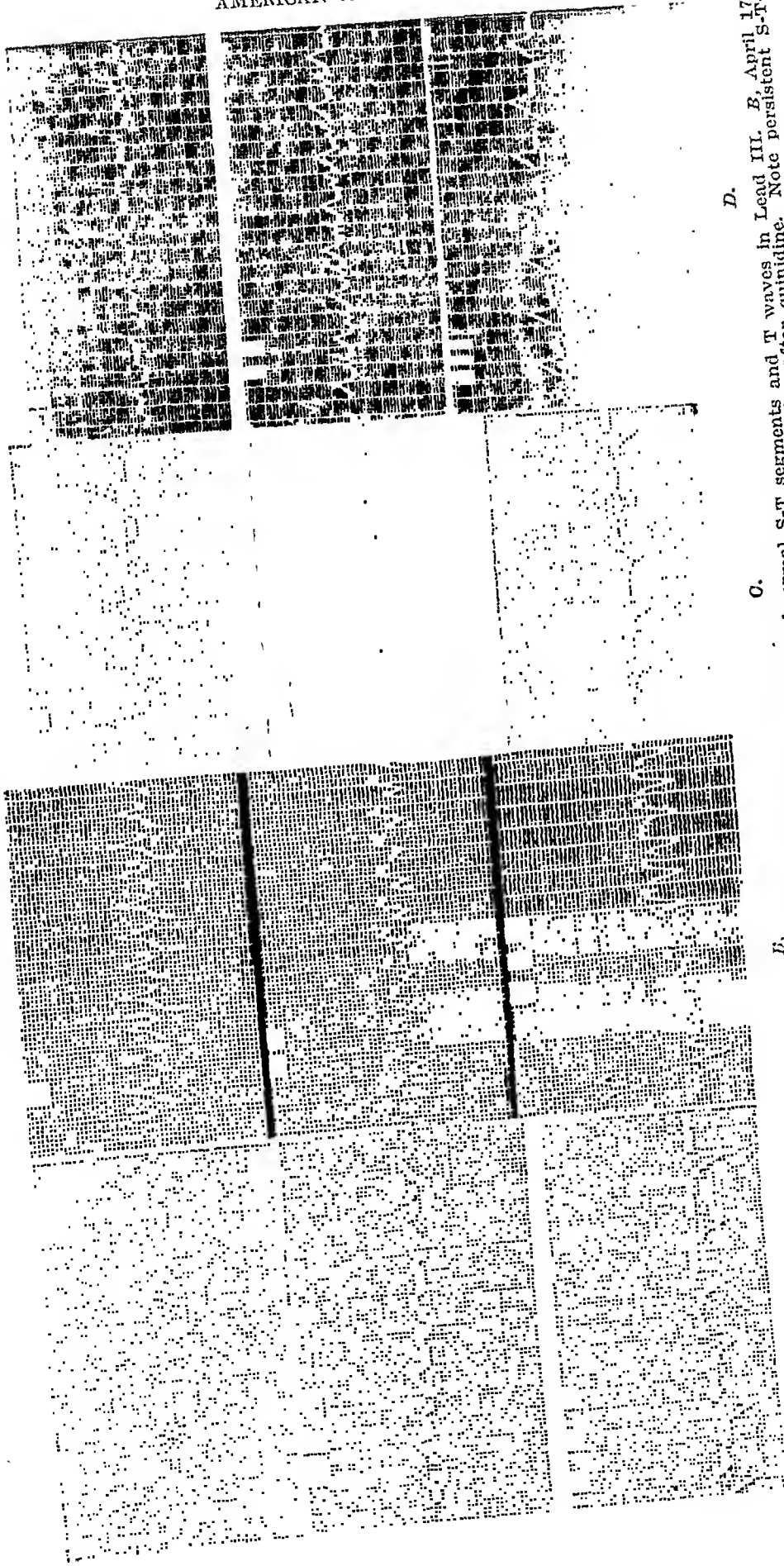


Fig. 5.—Roentgenogram of the chest, June 22, 1945. See text for detailed description. Erosion of lower ends of ribs (black arrows).

"that a spell was coming on." She remarked that the heart was pounding and beating very rapidly. An electrocardiogram taken at that time showed paroxysmal auricular tachycardia with a rate of 225 (Fig. 4, *B*). The child was given $\frac{3}{4}$ grain of quinidine sulfate and the mother was instructed to repeat this dosage every three hours until the heart rate slowed. However, within one hour after the initial dose of quinidine, the tachycardia disappeared. An electrocardiogram taken the next day showed a normal P-R interval and a normal duration of the QRS complex. The S-T-segment and T-wave abnormalities persisted in this tracing (Fig. 4, *C*). Since that time numerous spells of tachycardia have been aborted by the use of only $\frac{3}{4}$ grain of quinidine sulfate.

Physical examination of the child on June 22, 1945, revealed a slight bulge over the precordium and marked enlargement of the heart to the left on percussion. There was a moderate blowing systolic murmur at the pulmonic area and a slight systolic murmur at the apex. The aortic second sound and the pulmonic second sound were markedly accentuated. The blood pressure was 130/60 in the right arm and 120/60 in the left arm. The electrocardiogram was typical of the Wolff-Parkinson-White syndrome (Fig. 4, *D*). A roentgenogram of the chest on June 22, 1945 (Fig. 5), was interpreted by Dr. K. S. Davis,



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An interesting feature of the case presented here is the erosion of the ribs, as seen in the roentgenogram, occurring in a 3-year-old child. Roesler⁷ states that the youngest patient in whom this sign was reported was 6 years of age.

CONCLUSIONS

1. This report records the occurrence of the Wolff-Parkinson-White syndrome in an infant at the age of 14 weeks. This is apparently the youngest patient with this syndrome on record.

2. The occurrence of a congenital heart lesion in association with the Wolff-Parkinson-White syndrome is also reported.

3. Electrocardiograms showing the typical Wolff-Parkinson-White pattern and the paroxysmal auricular tachycardia associated with it are presented. The presence of a normal P-R interval and a normal QRS duration in some of the tracings shows that the cardiac impulse followed the normal conduction pathway through the heart some of the time.

4. The beneficial effect of quinidine sulfate in this case was demonstrated.

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St. Vincent's Hospital, as follows: "There is marked enlargement of the heart shadow especially in the region of the left ventricle. There is also seen some notching at the lower ends of the ribs and there is almost a complete absence of the shadow of the aortic arch. Roentgen diagnosis: Coarctation of the aorta."

DISCUSSION OF THE ELECTROCARDIOGRAMS

The first tracings, shown in Fig. 2, are, I believe, actually characteristic of the Wolff-Parkinson-White syndrome. The left axis deviation, S-T-segment changes, and T-wave abnormalities mentioned were all part of the pattern of bundle branch block. Certain features of this initial tracing were perhaps justifiably misinterpreted, for it is only by comparison with later tracings that one can recognize the pattern present. Levine⁵ has called attention to the errors made in the interpretation of electrocardiograms taken on infants. The restlessness and muscular activity of children and their movement of the lead wires cause many artifacts, which so distort the tracing that an accurate interpretation is often impossible. In this particular case, it was only after the child was old enough to cooperate that electrocardiograms were satisfactory enough to show the Wolff-Parkinson-White syndrome clearly (Fig. 3). Subsequent tracings revealed that at times the cardiac impulse followed the normal conduction pathway through the heart, as was evidenced by a normal P-R interval and a normal QRS duration (Fig. 4, *A*). The association of paroxysmal auricular tachycardia with this syndrome was demonstrated (Fig. 4, *B*). The pattern (Fig. 4, *B*) was seen to have reverted to a normal rate following the period of tachycardia on the previous day, after the administration of $\frac{3}{4}$ grain of quinidine sulfate (Fig. 4, *C*). The S-T-segment and T-wave abnormalities in this tracing were no doubt an aftereffect of the paroxysmal tachycardia.

COMMENTS

While the Wolff-Parkinson-White syndrome has been considered benign by most investigators, it is a generally accepted belief that paroxysms of tachycardia, to which these patients are susceptible, can cause heart failure and even lead to death. Any paroxysmal tachycardia which lasts long enough may lead to cardiac decompensation. Therefore, in those cases where cardiac disease coexists, the person prone to attacks of paroxysmal tachycardia is confronted with a definite hazard. The prognosis will vary with the ability of the physician or patient to stop the tachycardia promptly. Inability to terminate the rapid heartbeat will no doubt cause more rapid failure in an already diseased heart to which this load is added than in a normal heart. It is not unreasonable to state that the Wolff-Parkinson-White syndrome in association with a normal heart may be considered benign; however, its occurrence in association with other heart disease certainly alters the prognosis.

The Wolff-Parkinson-White syndrome has been attributed to the existence of an aberrant conduction bundle between the auricles and ventricles.⁶ If this theory be accepted, then we have in the case presented here not only an anomalous conduction system in the heart, but also a congenital heart lesion. This conclusion certainly would be in keeping with the well-known fact that congenital defects which occur are likely to be multiple.

The hyperactive carotid sinus reflex is frequently associated with numerous other pathologic conditions, both local and general.^{1, 5, 6} Weiss et al.¹ noted that "in 7 of 17 patients subject to the vagal type of syncope there was clinical evidence of degenerative change in the heart, and in the group as a whole there was a high incidence of generalized cardiovascular change." Sigler^{5, 6} pointed out that the hyperactive carotid sinus cardio-inhibitory reflex occurs most frequently and in highest degree in patients with coronary artery disease. He has graded the response on the basis of the degree of heart slowing, but apparently he did not commonly encounter syncope. In his opinion the hyperactive cardio-inhibitory reflex occurs with such frequency in these patients that testing for it aids in the diagnosis of coronary artery disease. Conversely, a syndrome simulating angina pectoris, without coronary artery disease, has also been reported as a manifestation of hyperactivity of the carotid sinus in the early reports of Weiss and his associates, and more recently by Friedman.⁷

The following case report is of unusual interest because both a hyperactive carotid sinus reflex and coronary arteriosclerosis are present and because the same symptoms were produced by both conditions and could not be differentiated.

CASE REPORT

A white officer, 48 years of age, was admitted to this General Hospital on Jan. 11, 1945, from overseas. His history dated back five months, at which time he was overseas when he developed shortness of breath on moderate exertion. Soon thereafter he developed bilateral frontal and parietal headaches, which were associated with exertion and were promptly relieved by rest. Later, he also began to have pain at the angles of both jaws. This pain also occurred with exertion and was promptly relieved by rest. Five weeks later he developed attacks of substernal pain associated with shortness of breath and a feeling of pressure on his chest, as well as pain in the jaws and head. These attacks were also precipitated by exertion and relieved by rest.

After a week or ten days of these attacks, on Oct. 7, 1944, while walking, he developed a severe substernal pain which radiated to the left posterior supra scapular area and was severe enough to cause him to break out in a cold sweat. The pain lasted about five minutes. Subsequently he was admitted to a hospital.

Physical examination at that time revealed no cardiac or other abnormality. The blood pressure was 130/74. Laboratory tests on several occasions showed the red blood cell count, hemoglobin, white blood cell count, differential, urinalysis, and sedimentation rate to be normal. X-ray examination showed a normal cardiac silhouette. An electrocardiogram taken the day following admission (Fig. 1, *a*) showed an inverted T₁ and a deeply inverted T₂, but no significant changes in the S-T segments. He was considered to have a coronary occlusion, and was treated with complete bed rest. During this time he had three mild attacks of substernal pressure with radiation to the left shoulder. One attack occurred while he was sitting on the edge of the bed, and another occurred while he was helping to make his bed. The attacks were quite brief and required no medication. A second electrocardiogram (Fig. 1, *b*) taken nine days after the first showed reversion of the T waves to their normal upright configuration. Subsequent electrocardiograms continued to show only left-axis deviation. A diagnosis of acute coronary thrombosis was made. After five weeks, evacuation was begun, first to Paris, subsequently to England. There, after a short period of bed rest, he was allowed up and around more freely.

While in a hospital in England, on Dec. 20, 1944, while lying in bed he developed another acute severe substernal pain, which again caused him to break out in a cold sweat. Again there was radiation to the left scapular region, but there was no associated jaw or head pain. This time the pain persisted for about one and one-half hours, and he was given an

A CASE REPORT OF SIMILAR SYMPTOMS PRODUCED BY HYPERACTIVE CAROTID SINUS REFLEX, ANGINA PECTORIS, AND MYOCARDIAL INFARCTION

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IN RECENT years the hyperactive carotid sinus reflex has received increasing clinical attention. Its mechanism and the syncopal syndrome produced by the vagal, depressor, or cerebral type of reflex have been thoroughly studied and described.¹⁻³ There have also been a number of reports of unusual symptomatology,⁴ although in most of these syncope is a prominent feature.

The numerous symptoms most frequently associated with this syndrome are mediated through the autonomic nervous system. These are summarized in Table I, which is taken from Ferris, Capps, and Weiss.²

TABLE I. SYMPTOMS DIRECTLY RELATED TO THE CAROTID SINUS MECHANISM

Carotid sinus reflex syncope may be: 1. Vagal type 2. Depressor type 3. Cerebral type		(Fainting, dizziness, weakness (Convulsions: contralateral bilateral
	Central	(Amnesia, cataplexy (Sleeplike state (Fatigue, weakness
	Ocular	(Pupillary changes (Strabismus (Lacrimation
	Respiratory	(Hyperpnea (Apnea (Yawning (Sighing
	Gastrointestinal	(Gaseous eructations (Nausea, vomiting (Increased peristalsis
	Vasomotor	(Hypotension (Peripheral constriction (Peripheral dilatation (Sweating
	Cardiac	(Bradycardia (Arrhythmia (Palpitation
	Extremities	(Numbness, tingling (Convulsions (Babinski's phenomenon

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†Major Glenn died on Dec. 21, 1945.

localized at the apex. The blood pressure was 130/80. The remainder of the examination, including that of the neck, was negative.

The results of laboratory studies were as follows: hemoglobin, 109 per cent; red blood cells, 4,860,000; white blood cells, 7,350; neutrophils, 53; lymphocytes, 45; eosinophils, 2. The sedimentation rate was 4 mm. per hour by the Wintrobe method. A Fishberg renal concentration test showed specific gravities of 1.028, 1.027, and 1.028. The urinalysis was essentially negative. The blood Kahn test was negative.

An electrocardiogram taken on admission showed merely a left axis deviation. An electrocardiogram taken after exercise revealed a sinus tachycardia of 120; otherwise there was no change.

The interpretation of the x-ray examination of the chest was: "The heart does not appear enlarged. Aorta is slightly elongated and tortuous, and there is a small calcareous plaque in the arch. The lungs appear clear."

During his first month in the hospital, the patient was ambulatory, without great limitation to his activity. He experienced three mild attacks of head and jaw pain, and slight shortness of breath. During or after these attacks he experienced palpitation. Exertion was not uniformly a precipitating factor.

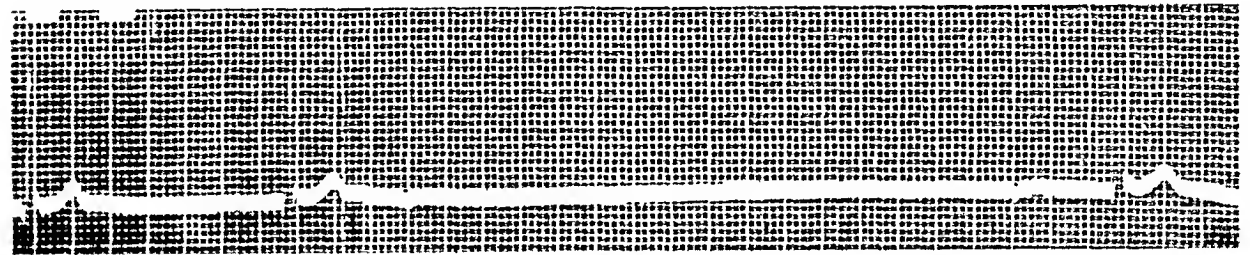


Fig. 2.—(Lead IVF) Asystole of 4.5 seconds' duration following right carotid sinus stimulation. Original rate was 85 per minute. (Date Feb. 10, 1945.)

On one occasion while the patient was being examined, it was noted that he had a somewhat flushed face, which appeared to be due to a tight collar on his shirt. This, together with the unusual symptomatology of jaw pain and head pain, suggested a possible hyperactive carotid sinus syndrome. With carotid pressure on either side, the patient spontaneously stated that symptoms of jaw pain and frontal headache similar to his previous symptoms were produced. At this time his pulse rate, which had been 60, dropped to 46 per minute.

Carotid sinus stimulation was subsequently employed on several occasions while electrocardiographic tracings were being taken and invariably produced attacks of pain of varying intensity. On each occasion stimulation of either carotid sinus produced a high degree of cardiac inhibition, though stimulation of the right sinus produced more slowing of the heart rate. The rate dropped from about 85 per minute to about 50 per minute. Fall in blood pressure (130/76 to 100/70) was transient and brief, and not uniformly produced. Syncope was never produced, even when stimulation was maintained for as long as sixty seconds. On one occasion while the right sinus was being stimulated, the patient had asystole lasting 4.5 seconds (Fig. 2) and experienced the most severe symptoms. He complained of head pain, jaw pain, dizziness, shortness of breath, and "tingling all over." All his symptoms were reproduced except the substernal pain.

The electrocardiogram (Fig. 2) during the 4.5-second asystole shows both sinus arrest and auriculoventricular block. No other changes were produced by the carotid sinus stimulation. There was little doubt that he had a hyperactive carotid sinus reflex of a type predominantly cardio-inhibitory (vagal).

These findings on carotid sinus stimulation made it difficult to determine whether all the symptoms were due to angina pectoris caused by coronary insufficiency and myocardial ischemia, or whether some or most of the symptoms were due to a hyperactive carotid sinus. The fact remained, however, that stimulation of the carotid sinus reproduced all symptoms except the substernal pain which the patient had had on previous occasions.

intravenous injection for relief. Unfortunately, although this was the most severe attack he had had, no electrocardiograms were taken. He left for the United States on December 23 and arrived at a hospital in this country on January 4, having had no symptoms in the interim. An electrocardiogram taken sixteen days after the severe attack showed only left axis deviation. The patient was then transferred to this General Hospital.

The family history revealed no cardiovascular or renal disease. His mother died at the age of 65 years from an unknown cause. His father was living and well at the age of 74 years.

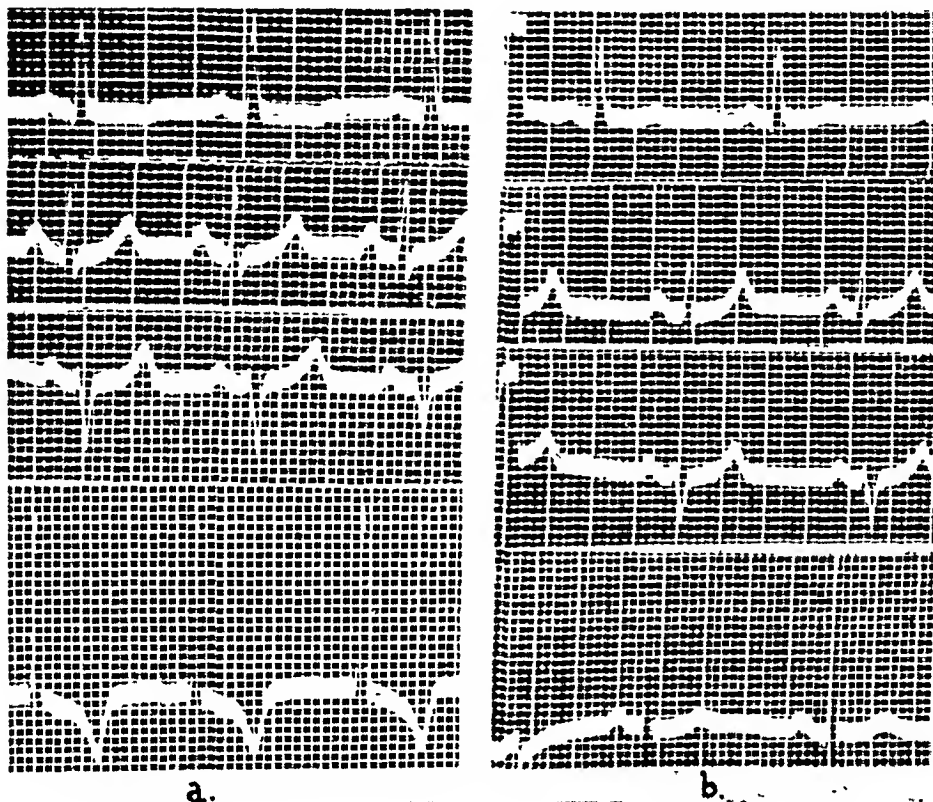


Fig. 1.—*a*, Electrocardiogram taken Oct. 8, 1944, twenty-four hours after first severe attack of substernal pain. Note inverted T_1 and T_4 . *b*, Electrocardiogram taken Oct. 17, 1944. The voltage of T_1 is slightly low, though in subsequent electrocardiograms it was entirely normal.

The patient had influenza complicated by pneumonia in 1918. He had a right herniorrhaphy in 1942. In January, 1944, he developed a left peroneal nerve palsy, for which he was being treated as an outpatient. One night when sitting by the fire he noticed that he had burned the calf of his left leg. The burn required hospital care, and during this time he received injections of thiamine and liver extract, following which the palsy gradually disappeared. During the two years previous to his present hospitalization, the patient had lost about 45 pounds in weight. This weight loss had been gradual and unassociated with any symptoms.

Physical examination at the time of admission to this hospital showed an individual who appeared to be older than his stated age. He was well developed and fairly well nourished, though he showed evidence of some weight loss. There was a scar from an old burn on the lateral aspect of his left leg. The ocular fundi showed a slight increase in tortuosity and streaking of the arteries. The brachial arteries were readily palpable but not tortuous. There was no apparent venous distention. The heart was of normal size. The sounds were slightly distant but of good quality. A_2 was louder than P_2 . No murmur was audible, but about one month after admission one observer noted a very soft systolic murmur

to a peak of 26 mm. per hour on the ninth day following the attack. Following this peak it returned to normal levels.

Electrocardiographic changes were characteristic of the Q_1T_1 anterior apical type of infarction. The record obtained on the morning after the acute episode (Fig. 3, *a*) showed a short Q_1 , elevation of the S- T_1 and S- T_4 segments, and slight depression of the S- T_2 and S- T_3 segments. T_1 and T_4 were deeply inverted. By March 6, the S-T segments had become isoelectric, but T_1 and T_4 had become more deeply inverted. This degree of inversion increased progressively and remained high until discharge (Fig. 3 *b*).

After the mild pains of the first few days, the clinical course was essentially asymptomatic. He was given phenobarbital and aminophylline three times daily. After three weeks of bed rest he was allowed up slowly and progressively. He remained asymptomatic except for slight tiredness after walking, but his strength rapidly returned. An x-ray film of the chest taken on March 29 showed a slight relative prominence of the left ventricular portion of the heart but was otherwise negative. He was discharged to his home on April 5, 1945.

DISCUSSION

There can be little doubt that while under our observation the patient had one quite typical myocardial infarction, probably the result of coronary occlusion on the basis of coronary arteriosclerotic disease. It is also probable that the episode just prior to his first hospitalization overseas represented more than a transient myocardial ischemia and may have been an infarction, though the only objective evidence to support this was the one electrocardiogram showing inverted T_1 and T_4 waves, which had become essentially normal, except for left axis deviation, in the electrocardiogram taken nine days later. Sixteen days following his second, and most severe, bout of pain overseas, an electrocardiogram was again, or still, normal except for left axis deviation.

The symptoms in these three attacks were similar to those in numerous other attacks he experienced during the month prior to overseas hospitalization and during his subsequent course under observation, except that the substernal pain was more severe. Many of these attacks were apparently precipitated by effort, though some definitely were not. Whether they represented attacks of true angina pectoris or hyperactive carotid sinus reflex is a matter for conjecture. They were not entirely typical of either, but had some of the features of both. The fact that stimulation of the carotid sinus region reproduced the symptoms indicates that this reflex at least was hyperactive, but there is also evidence that coronary disease was present. An infarction could hardly be attributed to a hyperactive carotid sinus (cardio-inhibitory) reflex.

To enter into a physiologic discussion of the mechanism of production of these symptoms in this particular case is beyond the scope of this paper. Suffice it to say that probably the same effector end organs were activated both by the reflexes initiated by myocardial ischemia and by the hyperactive carotid sinus reflex. Though the carotid sinus reflex is mentioned as one of the mechanisms affecting myocardial nutrition in Gross and Sternberg's report of 15 cases of myocardial infarction without demonstrable occlusion of the coronary arteries,⁸ this etiological factor has not been proved in any case. In discussing reflexes, Gross and Sternberg state: "Sudden death, which sometimes occurs, may be due to cardiac standstill resulting from extreme vagal stimulation, but it is

With some evidence of generalized arteriosclerosis, it was not at all improbable that the patient had coronary arteriosclerosis. He may have had a myocardial infarction which had produced only transient electrocardiographic changes and at this time showed no residual changes.

On Feb. 22, 1945, the patient appeared before an Army Retiring Board. Three days later he went fishing, in a motorboat. He had not exerted himself a great deal, but had been in the sun for several hours. Just before leaving the boat he was seized by a severe pain in the substernal region and felt pain also in the neck and in the jaws. Previous to returning to the hospital, within two hours of the attack, he had taken two nitroglycerin tablets, with some relief of his pain.

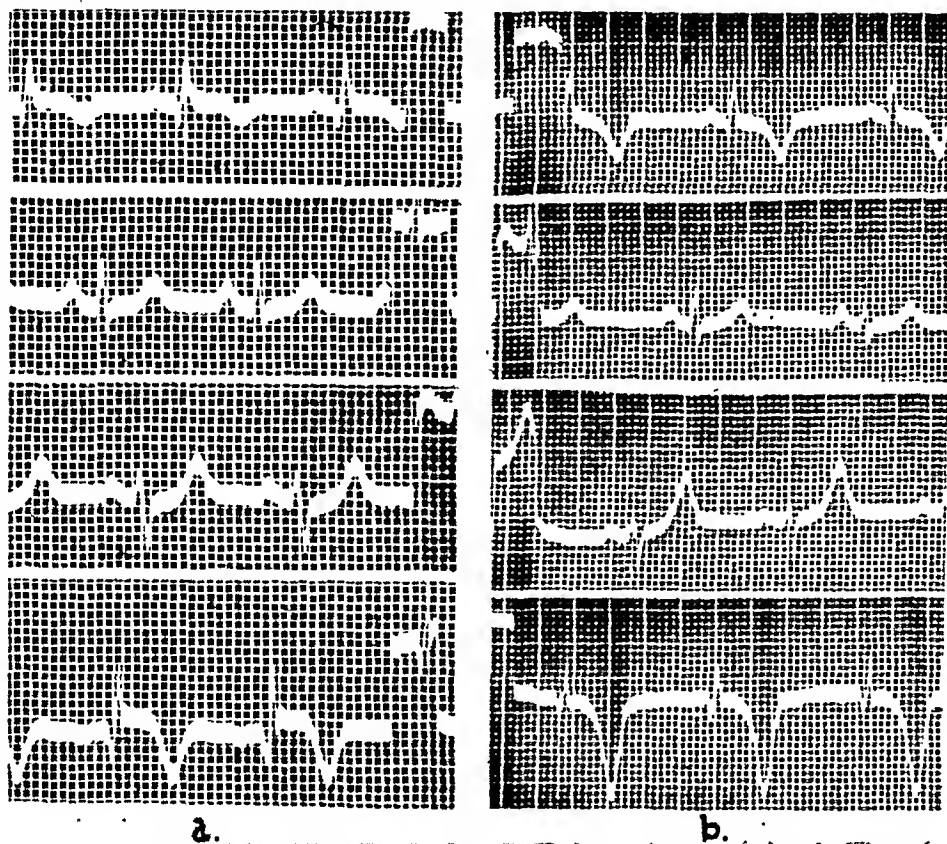


Fig. 3.—*a*, Electrocardiogram taken Feb. 26, 1945, twenty-four hours after a severe attack of substernal pain and pain in neck and jaws. *b*, Electrocardiogram taken April 2, 1945. The records are typical of acute (*a*) and residual (*b*) changes of anterior apical myocardial infarction.

On examination he had an anxious appearance. The pulse was regular and of good quality. The rate was 82 per minute. The examination of the heart was negative. The blood pressure was 138/92. Immediately after examination he was given $\frac{1}{4}$ grain of morphine and placed on bed rest. In about an hour and one-half a second dose of morphine was administered and the pain gradually disappeared, though he required another $\frac{1}{4}$ grain of morphine. He continued to have some aching and pressure in the precordial region for three to four days. Subsequently he had no complaints. Examinations of the heart after this acute episode were not significant. At no time was a friction rub heard, and at no time did the blood pressure fall below 120/80. The average was 136/80.

Laboratory studies on the day following this attack showed a white blood cell count of 10,150 per cubic millimeter, with a differential count of 82 per cent neutrophils and 18 per cent lymphocytes. The white count varied between 8,000 and 11,000 for the next four weeks. The sedimentation rate was 6 mm. per hour on the day following the attack and rose

Abstracts and Reviews

Selected Abstracts

Moses, W. R.: *The Early Diagnosis of Phlebothrombosis.* *New England J. Med.* 234: 288 (Feb. 28) 1946.

The high incidence of phlebothrombosis of the leg veins and the importance of early diagnosis are stressed. A simple clinical test is described for differentiating early phlebothrombosis from lesions simulating it. The test consists of two maneuvers. The first maneuver comprises a careful search for tenderness in the deep posterior calf by direct compression with the fingertips in the anteroposterior direction. The second maneuver consists in compressing the calf between the fingers and the palm in a lateral direction. In early phlebothrombosis this lateral compression is painless or relatively so, as compared with the first maneuver. The great majority of lesions simulating incipient thrombosis are accompanied by considerable tenderness on lateral compression. The findings in a case of peripheral neuritis, however, may be similar to those in a case of phlebothrombosis; accordingly, a brief neurological examination of the extremity is included as the third maneuver. NAIDE.

Lange, K., and Loewe, L.: *Subcutaneous Heparin in the Pitkin Menstruum for the Treatment of Experimental Human Frostbite.* *Surg., Gynec. & Obst.* 82: 256 (March) 1946.

Previous animal experimentation demonstrated that the timely use of heparin prevented gangrene, whereas untreated control animals uniformly developed gangrene as a result of experimentally induced frostbite. Only after at least seventy-two hours does organization of the erythrocytes occur in the smaller vessels. The use of heparin early in this prethrombotic stage prevents organized thrombi from forming. The authors applied these findings to a study of the use of heparin in eight human volunteers in whom artificial frostbite was produced. Small areas of frostbite were produced by the use of dry ice. Heparin in Pitkin's menstruum was deposited subcutaneously or intramuscularly. None of the volunteers developed any tissue loss while the control lesions showed central necrosis. The Pitkin menstruum was designed to regulate the release of water soluble drugs and is composed of gelatin, dextrose, glacial acetic acid, and water in definite proportions. NAIDE.

Stevens, C. D., Kotle, J. H., Smith, C. C., and McGuire, J.: *The Treatment of Human Hypertension With a Kidney Extract.* *Am. J. M. Sc.* 211: 227 (Feb.) 1946.

The authors report the treatment of four carefully controlled, hypertensive patients with a kidney extract which contained no renin or angiotoninase activity. A concentrated extract was prepared which was of relatively low toxicity.

Three of the patients showed during treatment a noteworthy fall in blood pressure, associated with fever. The fourth patient, who developed little fever, demonstrated only a slight depressor effect. However, blood pressure measurements made during the afternoon peak of the fever were not appreciably lower than those made in the morning before the temperature began to rise. The two subjects who demonstrated the greatest fall in blood pressure exhibited hypersensitivity reactions and developed serum precipitins. The fall in blood pressure during thiocyanate administration was of the same magnitude as that following the adminis-

also possible that such vagal stimulation may produce reflex coronary vasoconstriction and myocardial ischemia."

SUMMARY

1. A case report is presented in which a hyperactive carotid sinus reflex and coronary arteriosclerosis were present.
2. The fact that symptoms produced by stimulation of the carotid sinus were similar to the patient's spontaneous symptoms made it impossible to determine whether they were produced by the hyperactive carotid sinus reflex or were true angina pectoris resulting from myocardial ischemia.
3. During observation the patient had a typical myocardial infarction.

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therefore made of extrathoracic (chest wall) auscultation and intrathoracic auscultation in about 50 patients with normal hearts. About 20 were examined during the refilling of a therapeutic pneumothorax and the rest were examined during a pneumolysis. Before the operation was started, phonocardiograms were recorded from various points over the precordium. After refilling of a pneumothorax was finished, the needle used for the operation was connected directly with the recording microphone by a 3 to 4 cm. rubber tube. In the patients who had undergone pneumolysis, one of the two cannulae which are inserted after the Jacobaeus operation was closed, and the other was connected directly with the microphone. Simultaneous electrocardiograms were made.

It was found that the heart sounds inside the chest have a sonorous character with frequencies averaging 35 cycles per second in comparison with their high-pitched, metallic quality outside the chest where their frequencies are about 125 cycles per second for the first sound and 100 cycles for the second sound. The additional higher frequencies of the extrathoracic sounds are picked up while the sounds travel from the cardiac surface to the surface of the body.

The first heart sound in the intrathoracic pneumocardiogram consists usually of only four cycles representing, respectively, isometric contraction of the right and left ventricles and opening of the right and left semilunar valves. The first sound may be preceded by a ta-sound (single wave) which originates at the time of closing of the mitral valve. The second sound consists of two and, less frequently, three cycles, recording the closure of the two semilunar valves. The intrathoracic phonocardiogram frequently contains a third heart sound. This demonstrates that the latter actually originates in the heart. The auricular contraction sound preceding the first sound is also frequently seen.

LAPLACE.

Aikawa, J. K.: Hypersensitivity and Rheumatic Fever. *Ann. Int. Med.* 23: 969 (Dec.), 1945.

This study consists of a very extensive review of the literature pertaining to the relation of rheumatic fever to hypersensitivity.

Part I is concerned with hypersensitivity, antibodies, serum sickness, allergy, and the interrelation of these phenomena. The evolution of the concepts of this interrelationship is followed through successive reported studies, and the more recent concepts of various authors are presented.

Part II is concerned with the literature which presents evidence for a relation between hypersensitivity and the rheumatic process. The similarity between some manifestations of rheumatic disease and serum sickness is emphasized, as well as the general similarity between histologic changes in rheumatic disease and the proliferative inflammation of connective tissues found in sensitized animals following injection of the specific irritant. Included in the review are reports on the treatment of rheumatic subjects with salicylates and investigations which have been made to determine a rationale for such therapy in terms of immunologic reactions.

T. N. HARRIS.

Kety, S. S., and Schmidt, C. F.: The Effects of Active and Passive Hyperventilation of Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output and Blood Pressure of Normal Young Men. *J. Clin. Investigation* 25: 107 (Jan.), 1946.

Both active and passive hyperventilation by normal human subjects is accompanied by a diminution in cerebral blood flow amounting to 33 to 35 per cent (average) of the control volume flow. Carbon dioxide content, carbon dioxide tension, and hydrogen ion content of arterial blood diminish significantly, and the cerebral arteriovenous oxygen difference increases. During active hyperventilation cardiac output increases by an average of 2 per cent whereas during passive hyperventilation cardiac output decreases 11 per cent below the control values. Mean arterial pressure increases 12 per cent above the control during active hyperventilation and 8 per cent above the control during passive hyperventilation. It is of considerable interest that cerebral oxygen consumption is in-

tration of kidney extract in two cases but was not as marked as in the third patient whose blood pressure dropped.

The results obtained with this kidney extract do not recommend its use. Until the toxic effect of such kidney extracts can be eliminated, their therapeutic evaluation will be difficult and the mechanism of their action will be undetermined.

NAIDE.

Master, A. M., and Eichert, H.: *Functional Paroxysmal Auricular Fibrillation*. Am. J. M. Sc. 211: 336 (March) 1946.

By the term "uncomplicated or functional paroxysmal auricular fibrillation" is meant that type in which no evidence of organic heart disease can be demonstrated. This type of arrhythmia was not infrequently encountered in Naval personnel. The authors report a series of five cases in which the chief presenting symptom was "palpitation" or "pounding of the heart." They suggest that many cases which are diagnosed clinically as paroxysmal tachycardia are actually cases of paroxysmal auricular fibrillation. They also stress the importance of psychogenic or nervous factors in the production of paroxysmal auricular fibrillation. This was especially true among susceptible individuals who had been placed under unusual stress and strain.

From the standpoint of treatment, removal of the cause is important, particularly any factor disturbing the patient's mental equilibrium. Excessive exertion, mental and physical fatigue, lack of sleep, overindulgence in tobacco and coffee, and gastric distention should be avoided. They have obtained good results by the administration of digitalis or quinidine. In the absence of quinidine, they have administered potassium acetate, 1 or 2 Gm. three times daily. It is advisable that patients with this functional arrhythmia should be discharged from the Navy or retained for limited shore duty only.

BELLET.

Groedel, F. M., and Miller, M.: *Esophago-cardiogram*. Exper. Med. & Surg. 4: 26 (Feb.) 1946.

The esophagogram contains waves produced by the movements of the heart. It was studied as the esophago-cardiogram by the following technique. The tube of Einhorn's cardia dilator was introduced into the esophagus up to the cardia of the stomach, its outer end was connected with a microphone, and the system was filled with a few cubic centimeters of air. The microphone recorded on a three-string galvanometer simultaneously with Lead CR, and the heart sounds. The balloon was drawn out slowly, a record being made every 1 or 2 inches.

The esophago-cardiogram obtained with the balloon placed below the level of the left auricle is identical with the phlebogram obtained over the jugular bulb with a loaded receiver bell. It reflects most of the mechanical events occurring during auricular systole and diastole and ventricular systole. The action of the left auricle is represented by a positive a wave, produced by and reflecting the a wave of the vena cava. The ventriculodiastolic part of the esophago-cardiogram forms a v wave or a "v + d" wave. When the end of the tube is placed at or above the level of the auricle, the auricular wave is negative because the receiver balloon records here the movements of the auricular wall. The ta wave, representing probably the closure of the A-V valves, the b waves, caused by the isometric contractions of the ventricles, and the c complex, which reflects the isotonic contraction and ejection phase of the ventricles, are recorded throughout the esophagus.

LAPLACE.

Borchardt, P. R., and Groedel, F. M.: *Intrathoracic Auscultation in the Pneumothorax*. Exper. Med. & Surg. 4: 34 (Feb.) 1946.

In order to determine how the physical character of the heart sounds becomes altered while traveling from the cardiac surface to the surface of the chest, it is necessary to eliminate the lungs and the chest wall and study the heart sounds inside the thorax. Comparison was

(1) those in whom there was no suspicion of coronary heart disease, (2) those in whom coronary disease was suspected, and (3) those in whom the presence of coronary disease was very probable or certain. The criteria for a positive test were the same as those established by Levy and his associates in 1938. The technique employed was similar to that originally described by Levy and his co-workers, inhalation of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes, except for minor technical modifications of the apparatus which delivered the gas mixture. In attempting to correlate the clinical findings with the electrocardiographic changes produced by the hypoxemia tests, the records were interpreted without any knowledge of the clinical evidence. The incidence of positive tests in Groups 1, 2, and 3 was 3 per cent, 20 per cent, and 30 per cent, respectively. However, when the cases in which there were "coronary" cardiographic changes before the test were excluded from the calculation, the incidence of positive tests in Groups 1, 2, and 3 was 2 per cent, 18 per cent, and 23 per cent, respectively. It was also observed that the test was positive in only 5 of 18 patients who had healed myocardial infarction and still suffered from angina pectoris. In the opinion of the author the results appear to indicate that the value of this test in the diagnosis of coronary disease cannot yet be decided in any final sense at this time.

WENDKOS.

Lyons, R. H., and Burwell, C. S.: Induced Changes in the Circulation in Constrictive Pericarditis. *Brit. Heart J.* 8: 33 (Jan.), 1946.

The physiologic alterations and adaptations which accompany constriction of the pericardium were studied in two patients before and after pericardiectomy. An attempt was made to establish correlations between cardiac output, venous pressure, blood volume, circulation time, and heart rate. Spontaneous fluctuations in the level of the venous pressure, as well as sudden alterations of the venous pressure induced by rapid infusions or rapid phlebotomy, could be correlated only with blood volume and were found to bear no relationship to alterations in the heart rate or cardiac output. Further observations in one case following the alternate use of diuretics and sodium chloride seem to indicate that the elevated venous pressure, which is a conspicuous feature in constrictive pericarditis, is due to mechanisms similar to those which operate in cases of congestive failure without pericardial constriction, such as a rise in blood volume due to retention of sodium. The authors also speculate upon the adaptive mechanisms which occur in constrictive pericarditis and emphasize that a high venous pressure in this condition, unlike circumstances in which diastolic failure of the heart is due to tamponade by fluid in the pericardium, cannot be an effective compensation for the reduced cardiac output. On the other hand, the beneficial effect of tachycardia, either spontaneous or induced, is demonstrated from measurements of cardiac output and venous pressure. The authors also emphasize that since digitalis may induce slowing of the sinus rate, this drug is contraindicated in the treatment of constrictive pericarditis before adhesions are released.

WENDKOS.

Schnitzer, R., and Gutmann, D.: Myxedema With Pericardial Effusion. *Brit. Heart J.* 8: 25 (Jan.), 1946.

In a completely studied case of myxedema associated with marked enlargement of the heart shadow and with few signs or symptoms of cardiac failure, the authors present data which seemed to confirm the view of previous observers that part of the cardiac enlargement in "myxedema heart" is to be ascribed to an associated pericardial effusion. In their case, the presence of pericardial effusion was established by paracentesis with removal of 60 c.c. of straw-colored fluid from the left side of the pericardium. Serial electrocardiograms were made during the period of observation. The disappearance of the low voltage of all the electrocardiographic deflections in the standard limb leads and the return of the heart shadow to normal diameters following treatment with thyroid extract is explained by the authors as the result of dissipation of the fluid surrounding the

creased by 15 per cent above the control value during active hyperventilation whereas during passive hyperventilation the average change is 0 per cent. The increase in cerebral oxygen consumption during active hyperventilation is attributed to an increase in cerebral metabolic activity incident to the mental effort involved. The reduction in cerebral blood flow during hyperventilation is related to the diminution in carbon dioxide content of the blood thus produced.

FRIEDLAND.

Jager, B. V., and Alway, R.: The Treatment of Acute Rheumatic Fever With Large Doses of Sodium Salicylate, With Special Reference to Dose Management and Toxic Manifestations. *Am. J. M. Sc.* 211: 273 (March), 1946.

The results of the treatment of rheumatic fever by massive doses of sodium salicylate are evaluated. In the adult group of 18 patients, clinical and laboratory evidence of rheumatic activity appeared to vanish in six patients with initial attacks and in five of 12 patients with recurrent episodes. In all of the 18 adult patients, rapid symptomatic improvement occurred within a few days after therapy was begun. There was no fever after the end of the second week. Anemia, which was present in some cases at the time of admission, disappeared in every instance during therapy.

Good results were also obtained in a group of eight children but were not as striking as in the adult group. No serious intoxication appeared in any patient whose plasma salicylate level was less than 400 mg. per cubic centimeter. Some patients were able to tolerate levels above 500 mg. per cubic centimeter for prolonged periods without difficulty. In spite of significant prolongation of the prothrombin time, hemorrhagic manifestations were observed in only one instance.

BELLET.

Braun, K.: Paravertebral Block and the Electrocardiogram in Angina Pectoris. *Brit. Heart J.* 8: 47 (Jan.), 1946.

Considering the electrocardiogram as a method of evaluating the coronary circulation, the author studied the effect of block of the upper four thoracic paravertebral ganglia in a series of twelve patients who had angina pectoris. Four to seven injections were given at intervals of three to six days. The first injection utilized novocain, while the remainder consisted of novocain and alcohol. Electrocardiograms were taken before and after treatment, and, in seven cases, immediately before and twenty-four hours after the first injection.

Eleven patients had abnormalities of the electrocardiogram before treatment. In three instances, in which the abnormalities consisted, respectively, of bundle branch block, myocardial infarction, and negative T waves in all leads, there was no improvement in the electrocardiogram after block. In eight cases, improvement in the electrocardiogram occurred. Improvement was generally maximal at the end of treatment, although in four cases a positive effect was present twenty-four hours after the first block. The improvement could be explained by increase in coronary blood flow due either to a direct effect of the block or to abolition of reflex spasm accompanying the relief of pain. No consistent parallelism was found, however, between the improvement of the electrocardiogram and the persistence and severity of the anginal pain. In one case the electrocardiogram at first improved, then became more abnormal although the patient was relieved of pain; in other cases, the patients had recurrence of angina although the electrocardiogram improved.

LAPLACE.

Biorek, G.: Hypoxemia Tests in Coronary Disease. *Brit. Heart J.* 8: 17 (Jan.), 1946.

The subject of induction of electrocardiographic changes following the administration of low oxygen mixtures in the diagnosis of coronary artery disease is discussed. An analysis is presented of the results of 350 hypoxemia tests performed on 326 patients, of whom 166 were men and 160 were women. The patients were divided into three groups:

is suggestive of sinoauricular block in sinus rhythm. In the absence of any more precise explanation of its cause, this type of block may be regarded as a peculiarity of both the sinoauricular and auriculoventricular nodes.

LAPLACE.

Raynaud, R.: Hypertensive Accidents Following the Injection of Acetylcholine. Arch. d. mal. du cœur. 38: 217 (Sept.-Oct.) 1945.

The injection of acetylcholine has been found to occasionally produce transient hypertension. An instance of this reaction is reported in the case of a woman 63 years old. The patient had sustained a sudden left hemiplegia. A half hour later, the author administered an injection of 0.20 Gm. of acetylcholine. Within twenty minutes, the blood pressure increased from 140/80 to 220/120, and the patient had an attack of acute pulmonary edema. Venesection, sedation, and the intravenous administration of ouabain were followed by recovery and return of the blood pressure to its previous level.

The acetylcholine which was used in this case had been in the possession of the author for seven years. It is pointed out that although the characteristic action of acetylcholine is to lower the blood pressure, the drug may cause marked hypertension when it is no longer fresh. It is possible that acetylcholine may also elevate the blood pressure when given following the administration of atropine. The author has been unsuccessful, however, in eliciting this reaction in normal subjects. He emphasizes the danger involved in using old solutions of acetylcholine, deterioration of which was undoubtedly the cause of the serious complication encountered in his patient.

LAPLACE.

Berconsky, I., and Newman, J.: Mitral Stenosis and Arterial Hypertension. Rev. argent. de cardiol. 12: 94 (May-June) 1946.

In view of existing divergence of opinion regarding the significance of the co-existence of mitral stenosis and arterial hypertension, a study was made of 150 patients, 74 with mitral stenosis and 76 with mitral disease.

Arterial hypertension as indicated by a blood pressure of 150/90 or higher was present in 28 per cent of the total group. Its incidence among women was twice that encountered among men. In patients over 40 years of age the incidence of hypertension was 50 per cent. The association of mitral stenosis and hypertension appeared about twice as frequently among Jewish patients as compared with non-Jewish patients.

It is concluded from this study that arterial hypertension has the same incidence among patients who have mitral disease as occurs in the general population, and that the association therefore does not depend upon factors peculiar to the valvular disease.

LAPLACE.

Cohen, S. M.: The Surgical Management of Peripheral Vascular Disorders. Post-Grad. M. J. 22: 1 (Jan.) 1946.

This is a review of surgical procedures used in the treatment of spastic and organic arterial diseases, costoclavicular compression thrombosis, erythromelalgia, and posttraumatic painful states. Diagnostic methods used in the study of patients with peripheral vascular diseases are discussed. The usefulness of sympathectomy in the various disorders is evaluated.

NAIDE.

Cohen, S. M.: The Surgical Management of Peripheral Vascular Disorders. II. Vascular Trauma. Post-Grad. M. J. 22: 50 (Feb.) 1946.

This is a review of advances and trends in the treatment of vascular injuries. General rules regarding ligation following arterial injury are outlined. The management of the consequences of arterial contusion is described. The author reviews and describes his own approach to the management of traumatic arterial spasm, Volkmann's contracture, vascular repair and vein grafting, false aneurysm, and arteriovenous fistula. The management of the ischemic extremity in a patient who has suffered a vascular injury is outlined.

NAIDE.

heart. The amplitude of the auricular and ventricular deflections in the tracings made before, during, and after treatment with thyroid extract bore no relationship to the heart rate, the increase in voltage occurring without any cardiac acceleration. WENDKOS.

Lequieme, J., and Denolin, H.: Changes in the Coronary Circulation in the Course of Aortic Insufficiency in Young Subjects. *Arch. d. mal. du cœur.* 38: 225 (Sept.-Oct.) 1945.

Three cases are reported in which attacks of angina pectoris occurred in patients who had rheumatic aortic insufficiency. The patients were 14, 15, and 29 years old, respectively. The attacks of pain were independent of physical exertion and occurred most frequently at night. They were usually accompanied by tachycardia and increase in blood pressure. Electrocardiograms were made during the attacks and revealed transient S-T interval deviation similar to the changes induced by effort in patients who have coronary disease. The various explanations which have been offered as to the cause of anginal pain in the presence of aortic insufficiency are discussed. The author believes that his observations favor the view that the pain results from a disproportion between the coronary circulation and the work of the heart. LAPLACE.

Broustet, P., Bergouignan, M., and Leger, H.: Flutter and Auriculo-Ventricular Dissociation in a Patient With Myopathy. *Arch. d. du cœur.* 38: 212 (Sept.-Oct.) 1945.

The case is presented of a man, aged 54 years, who had long standing progressive muscular atrophy of idiopathic type. At an advanced stage of the disease but while he was still able to work, the patient began to have manifestations of cardiac insufficiency. A physician noted that the pulse rate was 40 per minute, the blood pressure was 220/110, and the heart was enlarged. After a month of treatment, the patient returned to work, but five months later he was admitted to the hospital because of two episodes of syncope. An electrocardiogram revealed auricular flutter with a rate of 200 per minute. The ventricular complexes were relatively normal but occurred at a rate of 40 per minute and had no constant time relationship to the auricular waves. There were no further manifestations of cardiac insufficiency and, when last observed, the patient had no symptoms except those caused by his muscular dystrophy. No subsequent change occurred in the electrocardiogram and even full digitalization failed to influence the constant auricular and ventricular rates. The cause of the heart disease responsible for the arrhythmia was not determined; the authors consider the possibility that it may have been related to the skeletal myopathy. LAPLACE.

Jourdan, F., Froment, R., Gallavardin, L., and Baud, A.: Three Observations on Chronic Experimental Nodal Rhythm by Surgical Ablation of the Sinus Node. *Arch. d. mal. du cœur.* 38: 197 (Sept.-Oct.) 1945.

The authors call attention to the fact that the criteria for the diagnosis of nodal bradycardia are variable and often uncertain. An investigation was therefore made which involved electrocardiographic studies on dogs in which surgical ablation of the sinus node had been performed. Two of the dogs were observed over a period of three to four years.

Variation of the P-R interval with wandering pacemaker occurred only in the first months after operation and could be caused to disappear by the injection of atropine. The phenomenon is regarded as an effect of vagal tonus and in that respect is comparable to sinus arrhythmia. Polymorphism of the P waves, however, was more or less constant and could not be abolished by atropine.

There occur occasionally in cases of pure nodal rhythm, blockage of the P waves and atypical ventricular complexes which are not premature and therefore suggest ventricular escape. Physiologic vagal tonus appears responsible for these anomalies. It seems indeed to exert a much more marked effect on nodal rhythm than it does on sinus rhythm. A more unusual occurrence is sudden doubling of the rate or an abrupt lengthy pause which

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INDEX TO VOLUME 31

AUTHORS INDEX

A

- Ashman, Richard. (*See* LaDue and Ashman), 685
Askey, John Martin. Hemiplegia following carotid sinus stimulation, 131

B

- Baggenstoss, Archie H. (*See* Keith, Pruitt, and Baggenstoss), 527
Batterman, Robert C., DeGraff, Arthur C., and Shorr, Harold M. Further observations on the use of mercupurin administered orally, 431
Bayley, Robert H. The electrocardiographic effects of injury at the endocardial surface of the left ventricle, 677
Bell, John W. (*See* York and Bell), 780
Bernstein, Arthur. (*See* Parsonnet, Bernstein, and Klosk), 769
— (*See* Parsonnet, Bernstein, and Martland), 438
— (*See* Parsonnet, Miller, Bernstein, and Klosk), 74
Bertacchi, Silvio. (*See* Pazzanese and Bertacchi), 33
Bidder, Thomas G. (*See* Kline and Bidder), 254
Blevins, Anne. (*See* Mac Neal, Blevins, and Duryee), 668
—, and Mac Neal, Ward J. Actinomyces septicus from human endocarditis, 663
Bodlander, Jerome W. The Wolff-Parkinson-White syndrome in association with congenital heart disease: coarctation of the aorta, 785
Brannon, E. S. (*See* Merrill, Warren, Stead, and Brannon), 413
—, Stead, E. A., Jr., Warren, J. V., and Merrill, A. J. Hemodynamics of acute hemorrhage in man, 407
— (*See* Warren, Brannon, Stead, and Merrill), 418
Brindley, Paul. (*See* Decherd, Ruskin, and Brindley), 352
Brown, Halla. (*See* Stewart, Evans, Haskell, and Brown), 617, 728
Brown, W. O. Myxoma of heart, 373
Budnitz, Joseph. (*See* Freed and Budnitz), 369
Burch, George E. (*See* Winsor and Burch), 387

C

- Carr, David T., and Essex, Hiram E. Certain effects of positive pressure respiration on the circulatory and respiratory systems, 53
Cole, Julia. (*See* Paul, Rhomberg, and Cole), 138
Cunningham, Robert S. Differences in blood pressure values determined by inflating and deflating the cuff of the sphygmomanometer, 220

D

- Dathe, Richard A., and Nathan, David A. Electrocardiographic changes resulting from phosphorus poisoning, 98
— (*See* Nathan and Dathe), 115
Decherd, George M., Jr., Ruskin, Arthur, and Brindley, Paul. Interatrial and sinoatrial block, with an illustrative case, 352
DeGraff, Arthur C. (*See* Batterman, DeGraff, and Shorr), 431
Dehn, Helmut, Feil, Harold, and Rinderknecht, Robert E. Electrocardiographic changes in cases of infectious hepatitis, 183
Drapiewski, John F. (*See* Medalia and Drapiewski), 103
Durgin, Bernice. (*See* Zimmerman and Durgin), 93
Duryee, A. Wilbur. (*See* Mac Neal, Blevins, and Duryee), 668

E

- Edelstein, Joseph M. Primary massive calcification with ossification of the myocardium, 496
Eichert, Herbert. Transient bundle branch block associated with tachycardia, 511
Essex, Hiram E. (*See* Carr and Essex), 53
Ethridge, Clayton B. (*See* Manchester and Ethridge), 633
Evans, Willis F. (*See* Stewart, Evans, and Haskell), 343
— (*See* Stewart, Evans, Haskell, and Brown), 617, 728

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Mac Neal. Ward J., Blevins, Anne, and Duryee, A. Wilbur. Clinical arrest of endocardial actinomycosis after forty-four million units of penicillin, 668

—, (See Blevins and Mac Neal), 663

Malinow, M. R., Katz, L. N., and Kondo, B. Is there a vagal pulmonocoronary reflex in pulmonary embolism? 702

Manchester, Benjamin, and Ethridge, Clayton B. An evaluation of the use of multiple versus single precordial leads, in conjunction with the three limb leads, for practical clinical electrocardiography, 633

Mann, Frank D. (See Flynn and Mann), 757

Martland, Harrison S. (See Parsonnet, Bernstein, and Martland), 438

Medalia, Leon S., and Drapiewski, John F. Congenital defect of the aortic vestibule complicated by bacterial endocarditis with perforation and death from cardiac tamponade, 103

Merrill, A. J. (See Brannon, Stead, Warren, and Merrill), 407

—, (See Warren, Brannon, Stead, and Merrill), 418

—, Warren, J. V., Stead, E. A., Jr., and Brannon, E. S. The circulation in penetrating wounds of the chest: a study by the method of right heart catheterization, 413

Meyers, Lawrence, and Poindexter, Charles A. A study of the prothrombin time in normal subjects and in patients with arteriosclerosis, 27

Miller, Ralph. (See Parsonnet, Miller, Bernstein, and Klosk), 74.

—, and Perelman, Julius S. Multiple disturbances of rhythm and conduction and unusual auricular T wave in a case of myocardial infarction, 501

Monroe, Willys M. Subacute bacterial endocarditis successfully treated with penicillin, 651

N

Nathan, David A., and Dathe, Richard A. Pericarditis with effusion following infections of the upper respiratory tract, 115

—, (See Dathe and Nathan), 98

P

Palatucci, Oscar A., and Knighton, James E. Spontaneous mediastinal emphysema, 364

Parsonnet, Aaron E., Bernstein, Arthur, and Klosk, Emanuel. Ventricular fibrillation, 769

—, Bernstein, Arthur, and Martland, Harrison, S. Massive left auricle with special reference to its etiology and mechanism, 438

—, Miller, Ralph, Bernstein, Arthur, and Klosk, Emanuel. Bigeminy, 74

Paul, W. D., Rhomberg, C., and Cole, Julia. Transitory A-V block occurring during scarlet fever, 138

Pazzanese, Dante, and Bertacchi, Silvio. Normal electrocardiograms in cardiovascular disease, 33

Perelman, Julius S. (See Miller and Perelman), 501

Poindexter, Charles A. (See Meyers and Poindexter), 27

Pruitt, Raymond D. (See Keith, Pruitt, and Baggenstoss), 527

Pullen, Roscoe L. (See Felknor and Pullen), 238

R

Read, Hilton S. (See Glenn and Read), 792

Reichsman, Francis. Studies on pathogenesis of pulmonary edema following bilateral vagotomy, 590

Rhomberg, C. (See Paul, Rhomberg, and Cole), 138

Rinderknecht, Robert E. (See Dehn, Feil, and Rinderknecht), 183

Ruskin, Arthur. (See Decherd, Ruskin, and Brindley), 352

Rutstein, David D. (See Thomson, Rutstein, Tolmack, and Walker), 565

S

Sarnoff, Stanley J. (See Luisada and Sarnoff), 270, 282, 293

Schlamowitz, Isadore. An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. I. The duration of the Q-T interval and its relationship to the cycle length (R-R interval), 329

—, An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. II. The duration of the T-P interval and its relationship to the cycle length (R-R interval), 464

—, An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. III. The duration of the P-R interval and its relationships to the cycle length (R-R interval), 473

Shorr, Harold M. (See Batterman, DeGraff, and Shorr), 431

Sprague, Howard B. The effects of malaria on the heart, 426

Stead, E. A., Jr. (See Brannon, Stead, Warren, and Merrill), 407

—, (See Merrill, Warren, Stead, and Brannon), 413

F

- Fauteux, Mercier. Treatment of coronary disease with angina by pericoromary neurectomy combined with ligation of the great cardiac vein, 260
- Feil, Harold. (*See* Dehn, Feil, and Rinderknecht), 183
- Felknor, George E., and Pullen; Roscoe L. Mumps myocarditis, 238
- Fertman, M. H., and Wolff, Louis. Calcification of the mitral valve, 580
- Flynn, Joseph E., and Mann, Frank D. The presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of the thebesian veins in cardiac failure from causes other than myocardial infarction, 757
- Fox, J. Robert. (*See* Herbut and Fox), 490
- Freed, Alexander N., and Budnitz, Joseph. Pure congenital pulmonary stenosis, 369
- Freundlich, J. Paroxysmal ventricular tachycardia, 557

G

- Gilbert, N. C. (*See* Kyser, Ginsberg, and Gilbert), 451
- Ginsberg, Harold. (*See* Kyser, Ginsberg, and Gilbert), 451
- Glenn, Paul M., and Read, Hilton S. A case report of similar symptom produced by hyperactive carotid sinus reflex, angina pectoris, and myocardial infarction, 792
- Goetz, Robert H. The rate and control of the blood flow through the skin of the lower extremities, 146

H

- Haskell, Helen S. (*See* Stewart, Evans and Haskell), 343
- (*See* Stewart, Evans, Haskell, and Brown), 617, 728
- Herbut, Peter A., and Fox, J. Robert. Persistent right aortic arch with atresia of the entire main pulmonary artery, 490
- Hollander, George. Electrocardiographic changes in scrub typhus fever, 481
- Howard, Frederick H. A method for the construction of the vectorcardiogram from the Einthoven electrocardiogram, 191
- A method for the orthodiagraphic measurement of the transverse diameter of the heart by means of the simple fluoroscope, 724
- Hussey, Hugh Hudson, Katz, Sol, and Yater. Wallace M. The superior vena caval syndrome; report of thirty-five cases, 1

K

- Katz, L. N. (*See* Malinow, Katz, and Kondo), 702
- Katz, Sol. (*See* Hussey, Katz, and Yater), 1
- Kay, Calvin F., and Livingood, Clarence S. Myocardial complications of cutaneous diphtheria, 744
- Keith, Norman M., Pruitt, Raymond D., and Baggenstoss, Archie H. Electrocardiographic changes in pericarditis associated with uremia, 527
- Kline, Edward M., and Bidder, Thomas G. A study of the subjective sensations associated with extrasystoles, 254
- Klosk, Emanuel. (*See* Parsonnet, Bernstein, and Klosk), 769
- (*See* Parsonnet, Miller, Bernstein, and Klosk), 74
- Knighton, James E. (*See* Palatucci and Knighton), 364
- Kondo, B. (*See* Malinow, Katz, and Kondo), 702
- Kyser, Franklin A., Ginsberg, Harold, and Gilbert, N. C. The effect of certain drugs upon the cardiotoxic lesions of digitalis in the dog, 451

L

- LaDue, John S., and Ashman, Richard. Electrocardiographic changes in acute glomerulonephritis, 685
- Levine, Harold D. Pathologic study of thirty-one cases of scrub typhus fever with especial reference to the cardiovascular system, 314
- Livingood, Clarence S. (*See* Kay and Livingood), 744
- Logue, Robert Bruce. (*See* Wallace and Logue), 223
- (*See* Wendkos and Logue), 711
- Luisada, Aldo A., and Sarnoff, Stanley J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. I. Effect of intra-arterial and intravenous infusions, 270
- and —. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. II. Mechanical and neurogenic elements, 282
- and —. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. III. Pharmacologic experiments, 293

M

- McDonald, Roger K. The coincidence of auricular fibrillation and bacterial endocarditis, 308
- Macht, David I. Thromboplastic properties of some mercurial diuretics, 460

SUBJECT INDEX*

A

- Abscess, brain, with congenital heart disease, 384*
- Acetylcholine and epinephrine, action of, on turtle ventricle, 381*
- effect of, on atropinized denervated heart, 382*
- hypertensive accidents following injection of, 805*
- Actinomyces septicus from human endocarditis (Blevins and Mac Neal), 663
- Actinomycosis, endocardial, clinical arrest of, after forty-four million units of penicillin (Mac Neal et al.), 66*
- Activity, physical, early, in rheumatic fever, therapeutic value of, preliminary report, 384*
- Adenomas, small, of adrenal cortex in hypertension and diabetes, 520*
- Anastomosis, observations relating to cardiac hypertrophy produced in rabbit by arteriovenous anastomosis, effect of closure of, 243*
- Anesthesia, ether, bilateral cervical vagotomy and sympathectomy in rat under (Reichsman), 595
- urethane, bilateral cervical vagotomy under (Reichsman), 599
- Angina pectoris and tobacco, 525*
- hyperactive carotid sinus reflex, and myocardial infarction, case report of similar symptoms produced by (Glenn and Read), 792
- paravertebral block and electrocardiogram in, 802*
- treatment of coronary disease with, by pericoronary neurectomy combined with ligation of great cardiac vein (Fauteux), 260
- Anginal syndrome, treatment of, with thiouracil, 247*
- Announcement, 113
- Aorta, coarctation and acute dissection of, associated with pregnancy, 247*
- congenital, and its surgical treatment, 381*
- surgical correction for, 380*
- Wolff-Parkinson-White syndrome in association with congenital heart disease (Bodlander), 785
- Aortic arch, persistent right, with atresia of entire main pulmonary artery (Herbut and Fox), 490
- insufficiency, changes in coronary circulation in course of, in young subjects, 804*
- vestibule, congenital defect of, complicated by bacterial endocarditis with perforation and death from cardiac tamponade (Medalia and Drapiewski), 103

- Arm, effect of change of position of, upon blood pressure (Stein), 477
- Arrhythmia, sinus, on cause of respiratory variation of ballistocardiogram, with note on, 659*
- Arterial pressure, pulmonary, in dogs, measurement of, 107*
- Arteriosclerosis, experimental; VIII. Effect of feeding olive oil on absorption and deposition of cholesterol, 381*
- study of prothrombin time in normal subjects and in patients with (Meyers and Poindexter), 27
- Arteriovenous anastomosis, effect of closure of anastomosis, observations relating to cardiac hypertrophy produced in rabbit by, 243*
- Artery, pulmonary, contribution to study of congenital dilatation of, 656
- entire main, persistent right aortic arch with atresia of (Herbut and Fox), 590
- Arthritis, rheumatoid, characteristic vascular pattern in patients with, 380*
- Asthenia, neurocirculatory, unstable T waves in Leads II and III in persons with (Wendkos and Logue), 711
- Atresia of entire main pulmonary artery, persistent right aortic arch with (Herbut and Fox), 490
- Atropinized denervated heart, effect of acetylcholine on, 382*
- Auricle, massive left, with special reference to its etiology and mechanism (Parsonnet et al.), 438
- Auricular fibrillation and bacterial endocarditis, coincidence of (McDonald), 308
- functional paroxysmal, 800*
- heart sounds, recognition and clinical significance of, 659*
- T wave, unusual, multiple disturbances of rhythm and conduction and, in case of myocardial infarction (Miller and Perelman), 501
- Auriculoventricular dissociation, flutter and, in patient with myopathy, 804*
- Auscultation, intrathoracic, in pneumothorax, 800*
- A-V block, transitory, occurring during scarlet fever (Paul et al.), 138

B

- Bacterial endarteritis, subacute, cure of, by surgical ligation in patient with patent ductus arteriosus complicated by presence of multiple congenital cardiac defects (Ziegler), 231
- endocarditis, coincidence of auricular fibrillation and (McDonald), 308

An asterisk () after a page number indicates the reference is an abstract and not an original article.

- , —, —, and —. (See Warren, Brannon, Stead, and Merrill), 418
- Stein, Irwin. The effects of change of position of the arm upon blood pressure, 477
- Stewart, Harold J., Evans, Willis F., and Haskell, Helen S. The peripheral blood flow under basal conditions in older male subjects with normal and elevated blood pressures, 343
- , —, —, and Brown, Halla. The effect of splanchnic resection on the peripheral blood flow and rectal and skin temperatures in hypertension, 728
- , —, —, and —. The peripheral blood flow and rectal and skin temperatures in hypertension, 617

T

- Thomson, K. Jefferson, Rutstein, David D., Tolmack, Daniel M., and Walker, William H. Electrocardiographic studies during and after pneumococcus pneumonia, 565
- Tolmack, Daniel M. (See Thomson, Rutstein, Tolmack, and Walker), 565

W

- Walker, William H. (See Thomson, Rutstein, Tolmack, and Walker), 565
- Wallace, Joseph J., and Logue, Robert Bruce. Metastatic carcinoma as a cause of constrictive pericarditis, 223
- Ward, Lawrence S. Abnormal electrocardiogram following recovery from paroxysmal tachycardia, 645

- Warren, J. V., Brannon, E. S., Stead, E. A., Jr., and Merrill, A. J. Pericardial tamponade from stab wound of the heart and pericardial effusion or empyema: a study utilizing the method of right heart catheterization, 418

—, —, —, and —. (See Brannon, Stead, Warren, and Merrill), 407

—, —, —, and —. (See Merrill, Warren, Stead, and Brannon), 413

- Wendkos, Martin H., and Logue, Robert Bruce. Unstable T waves in Leads II and III in persons with neuro-circulatory asthenia, 711

- Winsor, Travis, and Burch, George E. Use of the phlebomanometer; normal venous pressure values and a study of certain clinical aspects of venous hypertension in man, 387

- Wolff, Louis. (See Fertman and Wolff), 580

Y

- Yater, Wallace M. (See Hussey, Katz, and Yater), 1

- York, J. S., and Bell, John W. Fatal coronary failure without infarction: report of a case, 780

Z

- Ziegler, Robert F. The cure of subacute bacterial endarteritis by surgical ligation in a patient with patent ductus arteriosus complicated by the presence of multiple congenital cardiac defects, 231

- Zimmerman, Joseph J., and Durgin, Bernice. Staphylococcus aureus septicemia and pericarditis treated with penicillin, 93

Cardiae—Cont'd

- output, cerebral blood flow, cerebral oxygen consumption, and blood pressure of normal young men, effects of active and passive hyperventilation of. 801⁺
- in man, study of some of errors of right heart catheterization, 654⁺
- reaction to right and left pneumothorax, considerations of, 524⁺
- tamponade, congenital defect of aortic vestibule complicated by bacterial endocarditis with perforation and death from (Medalia and Drapiewski), 103
- vein, great, treatment of coronary disease with angina by pericoronary neurectomy combined with ligation of (Fauteux), 260
- Cardioinhibitory vagus endings in dog, blocking action of cinchona alkaloids and certain related compounds on, 242⁺
- Cardio-pulmonal function during pregnancy, 251 (B. Rev.)
- Cardiotoxic lesions of digitalis in dog, effect of certain drugs upon (Kyser et al.), 451
- Cardiovascular defects, congenital, physiopathology and surgical treatment of, 519⁺
- disease, normal electrocardiograms in (Pazzanese and Bertacchi), 33
- disturbances in tsutsugamushi disease, 248⁺
- receptors, paroxysmal pulmonary edema consequent to stimulation of; I. Effect of intra-arterial and intra-venous infusions (Luisada and Sarnoff), 270
- II. Mechanical and neurogenic elements (Luisada and Sarnoff), 282
- III. Pharmacologic experiments (Luisada and Sarnoff), 293
- system, gout and its effect on, 111⁺
- pathologic study of thirty-one cases of scrub typhus fever with especial reference to (Levine), 314
- Carotid shudder, 379⁺
- sinus, hyperactive, reflex, angina pectoris, and myocardial infarction. case report of similar symptoms produced by (Glenn and Read), 792
- stimulation, hemiplegia following (Askey), 131
- other cerebral disturbances following (Askey), 135
- Catheterization, right heart, study by method of; circulation in penetrating wounds of chest (Merrill et al.), 413
- study of some of errors in method of: cardiac output in man, 654⁺

Catheterization, right heart—Cont'd

- study utilizing method of; pericardial tamponade from stab wound of heart and pericardial effusion or empyema (Warren et al.), 418
- Cervical vagotomy, bilateral, and sympathectomy in rat under ether anesthesia (Reichsman), 595
- under urethane anesthesia (Reichsman), 599
- left, right thoracic and (Reichsman), 600
- Chest, circulation in penetrating wounds of; study by method of right heart catheterization (Merrill et al.), 413
- leads, configuration of epicardial and endocardial extrasystoles in, 655⁺
- Childhood, early, infancy and, pulse rate and blood pressure in, 378⁺
- precordial leads in; comment on presence of double upward deflections in leads from sternal region of normal children, 657⁺
- Children, Denver school, prevalence of rheumatic heart disease in, 250⁺
- prevention of rheumatic recurrences in, by use of sulfathiazole and sulfadiazine, 379⁺
- Cholesterol, effect of feeding olive oil on absorption and deposition of (VIII); experimental arteriosclerosis, 381⁺
- Cinchona alkaloids and certain related compounds, blocking action of, on cardioinhibitory vagus endings in dog. 242⁺
- Circulation, effects of malaria on (Sprague), 427
- failure in hunger edema, 383⁺
- in constrictive pericarditis, induced changes in, 803⁺
- in experimental neurogenic hypertension, 110⁺
- in penetrating wounds of chest; study by method of right heart catheterization (Merrill et al.), 413
- lying and standing, of tremor, and of program of bed exercises and early rising, studies of (I); convalescence of surgical procedures, 249⁺
- Circulatory and respiratory systems, certain effects of positive pressure respiration on (Carr and Essex), 53
- changes in burn shock, nature of, 524⁺
- Coarctation and acute dissection of aorta associated with pregnancy, 247⁺
- congenital, of aorta and its surgical treatment, 381⁺
- of aorta; experimental studies regarding its surgical correction, 112⁺
- surgical correction for, 380⁺
- Wolff-Parkinson-White syndrome in association with congenital heart disease (Bodlander), 785

Bacterial endocarditis—Cont'd

- ineffectiveness of penicillin in some cases of, 380*
- subacute, penicillin treatment of, 384*
- Streptococcus s. b. e.* in, 383*
- treated with penicillin (Monroe), 651
- with perforation and death from cardiac tamponade, congenital defect of aortic vestibule complicated by (Medalia and Drapiewski), 103

Ballistocardiogram, on cause of respiratory variation of, with note on sinus arrhythmia, 659*

Basal conditions, peripheral blood flow under, in older male subjects with normal and elevated blood pressures (Stewart et al.), 343

Bigeminal rhythm, persistent ventricular, in apparently normal hearts, 659*

rhythms, electrocardiographic (Parsonnet et al.), 75

Bigeminy (Parsonnet et al.), 74

Block, bundle branch, transient, associated with tachycardia (Eichert), 511

interatrial and sinoatrial, with illustrative case (Decherd et al.), 352

Blood flow, cerebral, cerebral oxygen consumption, cardiac output, and blood pressure of normal young men, effects of active and passive hyperventilation of, 801*

effect of body heating on (Goetz), 162

in peripheral vascular diseases (Goetz), 173

in sympathectomized extremities (Goetz), 168

peripheral, and rectal and skin temperatures in hypertension (Stewart et al.), 617

and rectal and skin temperatures in hypertension, effect of splanchnic resection on (Stewart et al.), 728

under basal conditions in older male subjects with normal and elevated blood pressures (Stewart et al.), 343

rate of, in toes (Goetz), 158

through skin of lower extremities, rate and control of (Goetz), 146

pressure and serum thiocyanate, relation of, 385*

cerebral blood flow, cerebral oxygen consumption, cardiac output and effects of active and passive hyperventilation of, 801*

effect of change of position of arm upon (Stein), 477

in hypertension, range of, 383*

of patients with hypertension and far-advanced renal disease, effect of high spinal anesthesia on—its possible relationship to pathogenesis of hypertension (V); studies in hypertension, 379*

Blood pressure—Cont'd

pulse rate and, in infancy and early childhood, 378*

values determined by inflating and deflating cuff of sphygmomanometer (Cunningham), 220

pressures, normal and elevated, peripheral blood flow under basal conditions in older male subjects with (Stewart et al.), 343

transfusion, intracardiac, 385*

volume determination, plasma and, in bilaterally vagotomized rats (Reichsman), 605

Body heating, effect of, on blood flow (Goetz), 162

Book reviews, 251, 661

Brain abscess with congenital heart disease, 384*

and heart, combined acute vascular lesions of, clinical-pathologic study of fifteen cases, 248*

Buerger's disease, 654*

Bundle branch block, transient, associated with tachycardia (Eichert), 511

Burn shock, nature of circulatory changes in, 524*

C

Calcification of mitral valve (Fertman and Wolff), 580

primary, massive, with ossification of myocardium (Edelstein), 496

Carcinoma, metastatic, as cause of constrictive pericarditis (Wallace and Logue), 223

Cardiac complications in infectious mononucleosis, electrographic evidence of, 655*

cycle in electrocardiograms of normal men, analysis of time relationships within (Schlamowitz), 329, 464, 473

damage, residual, question of, in scrub typhus (Levine), 326

defects, multiple congenital, cure of subacute bacterial endarteritis by surgical ligation in patient with patent ductus arteriosus complicated by presence of (Ziegler), 231

drive, venous return in absence of, 382*

dysfunction, relation of nutritional deficiency to, 525*

failure from causes other than myocardial infarction, presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins in (Flynn and Mann), 757

injury potential, development and contour of, 525*

E

- Edema, hunger, circulation failure in, 383⁻
 paroxysmal pulmonary, consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270, 282, 293
 pulmonary, following bilateral vagotomy, studies on pathogenesis of (Reichsman), 590
 general considerations on mechanism of (Luisada and Sarnoff), 303
- Effusion, pericardial, or empyema, pericardial tamponade from stab wound of heart and; study utilizing method of right heart catheterization (Warren et al.), 418
 pericarditis with, following infections of upper respiratory tract (Nathan and Dathe), 115
- Einthoven electrocardiogram, method for construction of vectorecardiogram from (Howard), 191
- Ejection, cardiac, action of, on venous return, 655⁻
- Electrocardiogram, abnormal, following recovery from paroxysmal tachycardia (Ward), 645
 abnormalities in, following hemolytic streptococcus sore throat, 658⁻
- Einthoven, method for construction of vectorecardiogram from (Howard), 191
 paravertebral block and, in angina pectoris, 802⁺
 prognostic value of, 661 (B. Rev.)
- Electrocardiogram, valor pronostico del, 661 (B. Rev.)
- Electrocardiograms in traumatic shock in man, 244⁺
 normal, in cardiovascular disease (Pazzanese and Bertacchi), 33
 of normal men, analysis of time relationships with cardiac cycle in; I. Duration of Q-T interval and its relationship to cycle length (R-R interval) (Schlamowitz), 329
 II. Duration of T-P interval and its relationship to cycle length (R-R interval) (Schlamowitz), 464
 III. Duration of P-R interval and its relationship to cycle length (R-R interval) (Schlamowitz), 473
- Electrocardiographic bigeminal rhythms (Parsonnet et al.), 75
 changes following heat stroke, 383⁺
 in acute glomerulonephritis (LaDue and Ashman), 685
 in cases of infectious hepatitis (Dehn et al.), 183
 in pericarditis associated with uremia (Keith et al.), 527
 in scrub typhus fever (Hollander), 481
 resulting from phosphorus poisoning (Dathe and Nathan), 98

Electrocardiographic—Cont'd

- effects of injury at endocardial surface of left ventricle (Bayley), 677
 studies during and after pneumococcus pneumonia (Thomson et al.), 565
- Electrocardiography, practical clinical, evaluation of use of multiple versus single precordial leads in conjunction with three limb leads for (Manchester and Ethridge), 633
- Electrogram of cardiac ventricle, action of heat and cold on different components of, 107⁺
- Emboli in retinal arteries, clinical differentiation of, from endarteritis, 245⁻
- Embolism, pulmonary, is there vagal monocroronary reflex in? (Malinow et al.), 702
 ligation of inferior vena cava for prevention of, 243⁺
- Emetine, effects of, on heart, 379⁺
- Emphysema, pulmonary, following prolonged positive pressure respiration (Carr and Essex), 68
 spontaneous mediastinal (Palatucci and Knighton), 364
- Empyema, pericardial effusion or, pericardial tamponade from stab wound of heart and; study utilizing method of right heart catheterization (Warren et al.), 418
- Encephalitis, meningo, rheumatic heart disease associated with, 113⁺
- Endarteritis, clinical differentiation of emboli in retinal arteries from, 245⁻
- Endocardial actinomycosis, clinical arrest of, after forty-four million units of penicillin (Mac Neal et al.), 668
 and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
 surface of left ventricle, electrocardiographic effects of injury at (Bayley), 677
- Endocarditis, bacterial, coincidence of auricular fibrillation and (McDonald), 308
 ineffectiveness of penicillin in some cases of, 380⁺
 with perforation and death from cardiac tamponade, congenital defect of aortic vestibule complicated by (Medalia and Drapiewski), 103
 enterococcal, clinical arrest in, 382⁻
 experimental, rheumatic-like and bacterial in rats, 111⁺
 human, *Actinomyces septicus* from (Blevins and Mac Neal), 663
 subacute bacterial, penicillin treatment of, 384⁻, (Monroe), 651, 658⁻
Streptococcus s.b.e. in, 383⁺

- Cold, heat and, action of, on electrogram of cardiac ventricle, 107*
- Conduction, multiple disturbances of rhythm and, unusual auricular T wave in case of myocardial infarction (Miller and Perelman), 501
- Congenital defect of aortic vestibule complicated by bacterial endocarditis with perforation and death from cardiac tamponade (Medalia and Drapiewski), 103
- heart disease, Wolff-Parkinson-White syndrome in association with: coarctation of aorta (Bodlander), 785
- Congestive heart failure, right ventricular, venous pressure in patients with (Winsor and Burch), 397
- Constrictive pericarditis, metastatic carcinoma as cause of (Wallace and Logue), 223
- Construction of vectorcardiogram from Einthoven electrocardiogram, method for (Howard), 191
- Control, rate and, of blood flow through skin of lower extremities (Goetz), 146
- Cor pulmonale, chronic, 522*
- Coronary artery disease among physicians, 243*
- circulation, changes in, in course of aortic insufficiency in young subjects, 804*
- disease, hypoxemia tests in, 802*
- with angina, treatment of, by pericoronary neurectomy, combined with ligation of great cardiac vein (Fauteux), 260
- failure, fatal, without infarction: report of case (York and Bell), 780
- thrombosis, acute, dicumarol in, 522*
- Cuff or sphygmomanometer, differences in blood pressure values determined by inflating and deflating (Cunningham), 220
- Curacao, Netherlands West Indies, occurrence of rheumatic carditis in native population of, 658*
- Cutaneous diphtheria, myocardial complications of (Kay and Livingood), 744
- Cycle, cardiac, in electrocardiograms of normal men, analysis of time relationships within (Schlamowitz), 329, 464, 473
- length (R-R interval), duration of P-R interval and its relationship to (Schlamowitz), 473
- duration of Q-T interval and its relationship to (Schlamowitz), 329
- duration of T-P interval and its relationship to (Schlamowitz), 464
- D
- Death following intravenous administration of papaverine hydrochloride, 243*
- perforation and, from cardiac tamponade, congenital defect of aortic vestibule complicated by bacterial endocarditis with (Medalia and Drapiewski), 103
- Death—Cont'd
- Defect, congenital, of aortic vestibule complicated by bacterial endocarditis with perforation and death from cardiac tamponade (Medalia and Drapiewski), 103
- Defects, congenital, following maternal rubella, 656*
- multiple congenital cardiac, cure of subacute bacterial endarteritis by surgical ligation in a patient with patent ductus arteriosus complicated by presence of (Ziegler), 231
- Degeneration, endocardial and subendocardial, mural thrombi, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Dehydration, salt depletion and, hemodynamic changes in, 660*
- Denver school children, prevalence of rheumatic heart disease in, 250*
- Diabetes, hypertension and, small adenomas of adrenal cortex in, 520*
- Diameter, transverse, of heart, method for orthodiagraphic measurement of, by means of simple fluoroscope (Howard), 724
- Dicumarol in acute coronary thrombosis, 522*
- Digitalis, effect of certain drugs upon cardiotoxic lesions of, in dog (Kyser et al.), 451
- Dilatation, congenital, of pulmonary artery, contribution to study of, 656*
- Diphtheria, cutaneous, myocardial complications of (Kay and Livingood), 744
- Dissection, acute, coarctation and, of aorta associated with pregnancy, 247*
- Disturbances, multiple, of rhythm and conduction and unusual auricular T wave in case of myocardial infarction (Miller and Perelman), 501
- Diuretics, mercurial; intolerance as shown by skin sensitivity, 378*
- thromboplastic properties of some (Macht), 460
- Drugs, certain, effect of, upon cardiotoxic lesions of digitalis in dog (Kyser et al.), 451
- Ductus arteriosus, patent, complicated by presence of multiple congenital cardiac defects, cure of subacute bacterial endarteritis by ligation in patient with (Ziegler), 231
- Dystrophy, progressive muscular, changes in musculature of gastrointestinal tract and in myocardium in, 242*

- Hemodynamics of acute hemorrhage in man (Brannon et al.), 407
- Hemolytic streptococcus sore throat, abnormalities in electrocardiogram following, 658*
- Hemorrhage, acute, in man, hemodynamics of (Brannon et al.), 407
or trauma of limbs, effects of positive pressure respiration on circulation and respiration when combined with (Carr and Essex), 64
- Hemorrhagic phenomena in scrub typhus (Levine), 325
shock; definition and criteria for its diagnosis, 660*
- Heparin, subcutaneous, in Pitkin menstruum for treatment of experimental human frostbite, 799*
- Hepatitis, infectious, electrocardiographic changes in cases of (Dehn et al.), 183
- Hyperactive carotid sinus reflex, angina pectoris, and myocardial infarction, case report of similar symptoms produced by (Glenn and Read), 792
- Hypersensitivity and rheumatic fever, 801*
- Hypertension and diabetes, small adenomas of adrenal cortex in, 520*
arterial, critical study of medical treatment of, 523*
mitral stenosis and, 805*
production of, by chronic renal artery-nerve stimulation, 246*
surgical treatment of, 521*
effect of splanchnic resection on peripheral blood flow and rectal and skin temperatures in (Stewart et al.), 728
essential, typical headache of; etiological considerations and report of new form of therapy, 250*
experimental neurogenic, circulation in, 110*
heart disease or, re-examination of veterans discharged because of, 520*
human, treatment of, with kidney extract, 799*
peripheral blood flow and rectal and skin temperatures in (Stewart et al.), 617
range of blood pressure in, 383*
sodium restriction in diet for, 112*
studies in; V. Effect of high spinal anesthesia on blood pressure of patients with hypertension and far-advanced renal disease—its possible relationship to pathogenesis of hypertension, 379*
venous, in man, normal venous pressure values and study of certain clinical aspects of; use of phlebomanometer (Winsor and Burch), 387
- Hypertensive accidents following injection of acetylcholine, 805*
cardiovascular disease, essential, in man, experiences with surgical treatment of, 245*
- Hypertrophy, cardiac, produced in rabbit by arteriovenous anastomosis, effect of closure of anastomosis, observations relating to, 243*
- Hypoxemia tests in coronary disease, 802*
- I
- In memoriam—Fred M. Smith, 253
- Infancy and early childhood, pulse rate and blood pressure in, 378*
- Infarction, fatal coronary failure without: report of case (York and Bell), 780
myocardial, case report of similar symptoms produced by hyperactive carotid sinus reflex, angina pectoris, and (Glenn and Read), 792
multiple disturbances of rhythm and conduction and unusual auricular T wave in case of (Miller and Perelman), 501
presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins in cardiac failure from causes other than (Flynn and Mann), 757
- Infections of upper respiratory tract, pericarditis with effusion following (Nathan and Dathe), 115
- Infectious hepatitis, electrocardiographic changes in cases of (Dehn et al.), 183
- Inferior vena cava, ligation of, for prevention of pulmonary embolism, 243*
- Infusions, intra-arterial and intravenous, effect of (I); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270
- Injury at endocardial surface of left ventricle, electrocardiographic effects of (Bayley), 677
potential, cardiac, development and contour of, 525*
- Insomnia due to left ventricular heart failure, 385*
- Inspiratory and expiratory resistance, rats breathing against (Reichsman), 603
resistance, rats breathing against (Reichsman), 601
- Interatrial and sinoatrial block, with illustrative case (Decherd et al.), 352
- Intolerance as shown by skin sensitivity: mercurial diuretics, 378*
- Intra-abdominal pressure and regulation of venous return, 107*

Enterococcal endocarditis, clinical arrest in, 382*

Epinephrine, acetylcholine and, action of, on turtle ventricle, 381*

Esophago-cardiogram, 800*

Ether anesthesia, bilateral cervical vagotomy and sympathectomy in rat under (Reichsman), 595

Etiology and mechanism, massive left auricle with special reference to (Parsonnet et al.), 438

Exercise, bed, and early rising, studies of circulation lying and standing, of tremor, and of (I); convalescence from surgical procedures, 249*

effect of, on size and shape of T wave (Dehn et al.), 188

step-up, on benches of different heights, pulse reaction to performing, 654*

test, mild, studies of various physiological responses to (II); convalescence from surgical procedures, 249*

Experiments, pharmacologic (III); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 293

Extrasystoles, epicardial and endocardial, configuration of, in chest leads, 655*

study of subjective sensations associated with (Kline and Bidder), 254

Extremities, lower, rate and control of blood flow through skin of (Goetz), 146

venous pressures in disorders of venous system of, 380*

sympathectomized, blood flow in (Goetz), 168

F

Fibrillation, auricular, and bacterial endocarditis, coincidence of (McDonald), 308

functional paroxysmal auricular, 800*

ventricular (Parsonnet et al.), 769

Fluoroscope, simple, method for orthodiagraphic measurement of transverse diameter of heart by means of (Howard), 724

Flutter and auriculoventricular dissociation in patient with myopathy, 804*

Frostbite, human, experimental subcutaneous heparin in Pitkin menstruum for treatment of, 799*

G

Gastrointestinal tract, changes in musculature of, and in myocardium in progressive muscular dystrophy, 242*

Glomerulonephritis, acute, electrocardiographic changes in (LaDue and Ashman), 685

Gout and its effect on cardiovascular system, 111*

H

Harveian olation on rheumatic fever and rheumatic heart disease, 246*

Headache, typical, of essential hypertension; etiological considerations and report of new form of therapy, 250*

Heart and other organs, pathologic changes in, in scrub typhus fever (Levine), 315

atropinized denervated, effect of acetylcholine on, 382*

brain and combined acute vascular lesions: of, clinical-pathologic study of fifteen cases, 248*

disease, congenital, brain abscess with, 384*

Wolff-Parkinson-White syndrome in association with: coarctation of aorta (Bodlander), 785

or hypertension, re-examination of veterans discharged because of, 520*

effects of emetine on, 379*

of malaria on (Sprague), 426

failure, congestive, in scrub typhus (Levine), 325

left ventricular, insomnia due to, 385*

right ventricular congestive, venous pressure in patients with (Winsor and Burch), 397

mechanism of action of jaundice on (Dehn et al.), 187

method for orthodiagraphic measurement of transverse diameter of, by means of simple fluoroscope (Howard), 724

myxoma of (Brown), 373

right, catheterization, circulation in penetrating wounds of chest (Merrill et al.), 413

pericardial tamponade from stab wound of heart and pericardial effusion or empyema (Warren et al.), 418

sounds, auricular, recognition and clinical significance of, 659*

stab wound of, and pericardial effusion or empyema, pericardial tamponade from; study utilizing method of right heart catheterization (Warren et al.), 418

tracheobronchial tree, and inferior vena cava of normal dogs, effects of positive pressure respiration on (Carr and Essex), 61

Hearts, apparently normal, persistent ventricular bigeminal rhythm in, 659*

Heat and cold, action of, on different components of electrogram of cardiac ventricle, 107*

stroke, electrocardiographic changes following, 383*

Hemiplegia following carotid sinus stimulation (Askey), 131

Hemodynamic changes in salt depletion and in dehydration, 660*

- Myocardium, musculature of gastrointestinal tract and, changes in, in progressive muscular dystrophy, 242⁻
 primary, massive calcification with ossification of (Edelstein), 496
 Myopathy, flutter and auriculoventricular dissociation in patient with, 804⁻
 Myxedema with pericardial effusion, 803⁻
 Myxoma of heart (Brown), 373

N

- Neurectomy, pericoronary (Fauteux), 263
 combined with ligation of great cardiac vein, treatment of coronary disease with angina by (Fauteux), 260
 Neurocirculatory asthenia, unstable T waves in Leads II and III in persons with (Wendkos and Logue), 711
 Neurogenic, mechanical and, elements (II); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 282
 Nodal rhythm, chronic experimental, three observations on, by surgical ablation of sinus node, 804⁻
 Nodules in rheumatic fever, 110⁻
 Normal men, analysis of time relationships within cardiac cycle in electrocardiograms (Schlamowitz), 329, 464, 473
 Nutritional deficiency, relation of, to cardiac dysfunction, 525⁻

O

- Olive oil, effect of feeding, on absorption and deposition of cholesterol (VIII); experimental arteriosclerosis, 381
 Orthodiagraphic measurement of transverse diameter of heart, method for, by means of simple fluoroscope (Howard), 724
 Ossification of myocardium, primary, massive calcification with (Edelstein), 496
 Oxygen consumption, cerebral, cerebral blood flow, cardiac output, and blood pressure of normal young men, effects of hyperventilation of, 801⁻

P

- P wave, pulmonary, comparative study of, in chronic mitral and pulmonary disease, 108⁻
 Papaverine hydrochloride, death following intravenous administration of, 243⁻
 Paravertebral block and electrocardiogram in angina pectoris, 802⁻

- Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270, 282, 293
 tachycardia, abnormal electrocardiogram following recovery from (Ward), 645
 ventricular tachycardia (Freudlich), 557
 Patent ductus arteriosus complicated by presence of multiple congenital cardiac defects, cure of subacute bacterial endarteritis by surgical ligation in patient with (Ziegler), 231
 surgical therapy of, 110⁻
 Pathogenesis of pulmonary edema following bilateral vagotomy, studies on (Reichsman), 590
 Pathologic study of thirty-one cases of scrub typhus fever with especial reference to cardiovascular system (Levine), 314
 Penetrating wounds of chest, circulation in; study by method of right heart catheterization (Merrill et al.), 413
 Penicillin, clinical arrest of endocardial actinomycosis after forty-four million units of (Mac Neal et al.), 668
 ineffectiveness of, in some cases of bacterial endocarditis, 380⁻
 intrapericardial, pneumococcal pericarditis treated with, 381⁻
 Staphylococcus aureus septicemia and pericarditis treated with (Zimmerman and Durgin), 93
 treatment of subacute bacterial endocarditis, 384⁻ (Monroe), 651, 658⁻
 Perforation and death from cardiac tamponade, congenital defect of aortic vestibule complicated by bacterial endocarditis with (Medalia and Drapiewski), 103
 Pericardial effusion, myxedema with, 803⁻
 or empyema, pericardial tamponade from stab wound of heart and (Warren et al.), 418
 tamponade from stab wound of heart and pericardial effusion or empyema (Warren et al.), 418
 Pericarditis associated with uremia, electrocardiographic changes in (Keith et al.), 527
 constrictive, induced changes in circulation in, 803⁻
 metastatic carcinoma as cause of (Wallace and Logue), 223
 pneumococcal, treated with intrapericardial penicillin, 381⁻
 Staphylococcus aureus septicemia and, treated with penicillin (Zimmerman and Durgin), 93
 with effusion following infections of upper respiratory tract (Nathan and Dathe), 115

- Intra-arterial infusions, effect of (I); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270
- Intravenous, infusions, effect of (I); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 270
- J
- Jaundice, mechanism of action of, on heart (Dehn et al.), 187
- K
- Kidney extract, treatment of human hypertension with, 799*
- L
- Leads II and III, unstable T waves in, in persons with neurocirculatory asthenia (Wendkos and Logue), 711
- chest, configuration of epicardial and endocardial extrasystoles in, 655*
- precordial, in childhood; comment on presence of double upward deflections in leads from sternal region of normal children, 657*
- multiple versus single, evaluation of use of, in conjunction with three limb leads, for practical clinical electrocardiography (Manchester and Ethridge), 633
- Lesions, cardiotoxic, of digitalis in dog, effect of certain drugs upon (Kyser et al.), 451
- Letters, 377
- Ligation of great cardiac vein, treatment of coronary disease with angina by pericoronary neurectomy combined with (Fauteux), 260
- coronary vein in man (Fauteux), 261
- Limb leads, three, evaluation of use of multiple versus single precordial leads in conjunction with, for practical clinical electrocardiography (Manchester and Ethridge), 633
- Lower extremities, rate and control of blood flow through skin of (Goetz), 146
- M
- Malaria, effects of, on heart (Sprague), 426
- Maternal rubella, congenital defects following, 656*
- Mechanical and neurogenic elements (II); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 282
- Mechanism, etiology and, massive left auricle with special reference to (Parsonnet et al.), 438
- Mediastinal emphysema, spontaneous (Palatucci and Knighton), 364
- Medical treatment of arterial hypertension, critical study of, 523*
- Meningo encephalitis, rheumatic heart disease associated with, 113*
- Mercupurin administered orally, further observations on use of (Batterman et al.), 431
- Mercurial diuretics; intolerance as shown by skin sensitivity, 378*
- thromboplastic properties of some (Macht), 460
- Metastatic carcinoma as cause of constrictive pericarditis (Wallace and Logue), 223
- Method for construction of vectorcardiogram from Einthoven electrocardiogram (Howard), 191
- Mitral valve, calcification of (Fertman and Wolff), 580
- Mononucleosis, infectious, electrographic evidence of cardiac complications in, 655*
- Morgagni-Adams-Stokes syndrome, special reference to; ventricular fibrillation (Parsonnet et al.), 769
- Mumps (epidemic parotitis), acute myocarditis in, 523*
- myocarditis (Felknor and Pullen), 238
- Mural thrombi, endocardial and subendocardial degeneration, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Musculature of gastrointestinal tract, changes in, and in myocardium in progressive muscular dystrophy, 242*
- Myocardial complications of eutaneous diphtheria (Kay and Livingood), 744
- infarction, case report of similar symptoms produced by hyperactive carotid sinus reflex, angina pectoris, and (Glenn and Read), 792
- multiple disturbances of rhythm and conduction and unusual auricular T wave in case of (Miller and Perelman), 501
- presence and pathogenesis of endocardial and subendocardial degeneration, mural thrombi, and thromboses of thebesian veins in cardiac failure from causes other than (Flynn and Mann), 757
- Myocarditis, acute, in mumps (epidemic parotitis), 523*
- nonspecific, 112*
- mumps (Felknor and Pullen), 238

Q

- Q-T interval, duration of, and its relationship to cycle length (R-R interval) (I); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 329

R

- Rate and control of blood flow through skin of lower extremities (Goetz), 146
- Raynaud's disease, part of venospasm in producing clinical picture of, 532*
- Receptors, cardiovascular, paroxysmal pulmonary edema consequent to stimulation of (Luisada and Sarnoff), 270, 282, 293
- Rectal and skin temperatures, effect of splanchnic resection on peripheral blood and, in hypertension (Stewart et al.), 728
- in hypertension, blood flow and (Stewart et al.), 617
- Resection, splanchnic effect of, on peripheral blood flow and rectal and skin temperatures in hypertension (Stewart et al.), 728
- Respiration, positive pressure, certain effects of, on circulatory and respiratory systems (Carr and Essex), 53
- Respiratory and circulatory systems, certain effects of positive pressure respiration on (Carr and Essex), 53
- tract, upper, pericarditis with effusion following (Nathan and Dathe), 115
- Rheumatic carditis, occurrence of, in native population of Curacao, Netherlands West Indies, 658*
- fever, acute, treatment of, with large doses of sodium salicylate, with special reference to dose management and toxic manifestations, 802*
- and rheumatic heart disease, Harveian oration on, 246*
- effect of salicylate therapy on Weltmann serum coagulation reaction and its use as prognostic test in, 656*
- etiology and pathogenesis of, 244*
- hypersensitivity and, 801*
- nodules in, 110*
- observations on treatment of, with vitamin P, 244*
- streptococcus infection and, some experimental aspects of, 110*
- studies in, 109*
- therapeutic value of early physical activity in, preliminary report, 384*
- heart disease associated with meningo-encephalitis, 113*
- Rheumatic heart disease—Cont'd
- Harveian oration on rheumatic fever and, 246*
- in Denver school children, prevalence of, 250*
- recurrences in children, prevention of, by use of sulfathiazole and sulfadiazine, 379*
- Rheumatoid arthritis, characteristic vascular pattern in patients with, 380*
- Rhythm and conduction, multiple disturbances of, and unusual auricular T wave in case of myocardial infarction (Miller and Perelman), 501
- bigeminal, persistent ventricular, in apparently normal hearts, 659*
- R-R interval, cycle length, duration of P-R interval and its relationship to (Schlamowitz), 473
- duration of Q-T interval and its relationship to (Schlamowitz), 329
- duration of T-P interval and its relationship to (Schlamowitz), 464
- Rubella, maternal, congenital defects following, 256*

S

- Salicylate therapy, effect of, on Weltmann serum coagulation reaction and its use as prognostic test in rheumatic fever, 656
- Salt depletion and dehydration, hemodynamic changes in, 660*
- Scarlet fever, transitory A-V block occurring during (Paul et al.), 138
- Scrub typhus, congestive heart failure in (Levine), 325
- fever, electrocardiographic changes in (Hollander), 481
- pathologic study of thirty-one cases of, with especial reference to cardiovascular system (Levine), 314
- hemorrhagic phenomena in (Levine), 325
- pathologic changes in heart and other organs in (Levine), 315
- question of residual cardiac damage in (Levine), 326
- Sensations, subjective, associated with extrasystoles, study of (Kline and Bidder), 255
- Septicemia, Staphylococcus aureus, and pericarditis treated with penicillin (Zimmerman and Durgin), 93
- Serum thiocyanate, relationship of blood pressure and, 385*
- Shape, size and, of T wave, effect of exercise on (Dehn et al.), 188

- Pericoronary neurectomy (Fauteux), 263
combined with ligation of great cardiac vein, treatment of coronary disease with angina by (Fauteux), 260
- Peripheral blood flow and rectal and skin temperatures in hypertension (Stewart et al.), 617
effect of splanchnic resection on (Stewart et al.), 728
under basal conditions in older male subjects with normal and elevated blood pressures (Stewart et al.), 343
vascular diseases, blood flow in (Goetz), 173
- Pharmacologic experiments (III); paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors (Luisada and Sarnoff), 293
- Phlebomanometer, use of: normal venous pressure values and study of certain clinical aspects of venous hypertension in man (Winsor and Burch), 387
- Phlebothrombosis, early diagnosis of, 799
- Phosphorus poisoning, electrocardiographic changes resulting from (Dathe and Nathan), 98
- Physicians, coronary artery disease among, 243*
- Physiological responses, various, to mild exercise test, studies of (II); convalescence from surgical procedures, 249*
- Physiopathology and surgical treatment of congenital cardiovascular defects, 519*
- Plasma and blood volume determination in bilaterally vagotomized rats (Reichsman), 605
- Plethysmogram of toes during rest (Goetz), 148
- Pneumococcal pericarditis treated with intrapericardial penicillin, 381*
- Pneumococcus pneumonia, electrocardiographic changes during and after (Thomson et al.), 565
- Pneumonia, pneumococcus, electrocardiographic studies during and after (Thomson et al.), 565
- Pneumopericardium, 246*
- Pneumothorax, intrathoracic auscultation in, 800*
right and left, considerations of cardiac reaction to, 524*
- Poisoning, phosphorus, electrocardiographic changes resulting from (Dathe and Nathan), 98
- Polyarteritis nodosa, 520*
- Position of arm, effect of change of, upon blood pressure (Stein), 477
- Positive pressure respiration, certain effects of, on circulatory and respiratory systems (Carr and Essex), 53
- P-R interval, duration of, and its relationship to cycle length (R-R interval) (III); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 473
- Precordial leads in childhood; comment on presence of double upward deflections in leads from sternal region of normal children, 657*
multiple versus single, evaluation of use of, in conjunction with three limb leads, for practical clinical electrocardiography (Manchester and Ethridge), 633
- Pregnancy, cardiopulmonary function during, 251 (B. Rev.)
coarctation and acute dissection of aorta associated with, 247*
- Prothrombin time in normal subjects and in patients with arteriosclerosis, study of (Meyers and Poindexter), 27
variations in (Meyers and Poindexter), 29
- Pulmonary arterial pressure in dogs, measurement of, 107*
artery, contribution to study of congenital dilatation of, 656*
entire main, persistent right aortic arch with atresia of (Herbut and Fox), 490
edema following bilateral vagotomy, studies on pathogenesis of (Reichsman), 590
general considerations on mechanism of (Luisada and Sarnoff), 303
paroxysmal, consequent to stimulation of cardiovascular receptors; I. Effect of intra-arterial and intravenous infusions (Luisada and Sarnoff), 270
II. Mechanical and neurogenic elements (Luisada and Sarnoff), 282
III. Pharmacologic experiments (Luisada and Sarnoff), 293
embolism, is there vagal pulmonocoronary reflex in? (Malinow et al.), 702
ligation of inferior vena cava for prevention of, 243*
stenosis, pure congenital (Freed and Budnitz), 369
- Pulmonocoronary reflex, vagal, in pulmonary embolism? (Malinow et al.), 702
- Pulse rate and blood pressure in infancy and early childhood, 378*
reaction to performing step-up exercise on benches of different heights, 654*

- Sympathotomy, bilateral cervical vagotomy and, in rat under ether anesthesia (Reichsman), 595
- Syndrome, anginal, treatment of, with thiouracil, 247*
- superior vena cava; report of thirty-five cases (Hussey et al.), 1
- Wolff-Parkinson-White, and related problems, 108*
- System, cardiovascular, pathologic study of thirty-one cases of scrub typhus fever with especial reference to (Levine), 314
- Systems, circulatory and respiratory, certain effects of positive pressure respiration on (Carr and Essex), 53
- T
- T waves, unstable, in Leads II and III in persons with neurocirculatory asthenia (Wendkos and Logue), 711
- unusual auricular, multiple disturbances of rhythm and conduction and, in case of myocardial infarction (Miller and Perelman), 501
- Tachycardia, paroxysmal, abnormal electrocardiogram following recovery from (Ward), 645
- ventricular (Freundlich), 557
- transient bundle branch block associated with (Eichert), 511
- ventricular—report on ten cases, eight of which were treated with quinidine with recovery in seven, 111
- Tamponade, cardiac, congenital defect of aortic vestibule complicated by bacterial endocarditis with perforation and death from (Medalia and Drapiewski), 103
- pericardial, from stab wound of heart and pericardial effusion or empyema; study utilizing method of right heart catheterization (Warren et al.), 418
- Temperatures, rectal and skin, effect of splanchnic resection on peripheral blood flow and, in hypertension (Stewart et al.), 728
- in hypertension, peripheral blood flow and (Stewart et al.), 617
- Tetralogy of Fallot, case of, 109*
- Thebesian veins, thromboses of, endocardial and subendocardial degeneration, and mural thrombi, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Therapeutic value of early physical activity in rheumatic fever, preliminary report, 384*
- Thiocyanate, serum, relationship of blood pressure and, 385*
- Thiouracil, treatment of anginal syndrome with, 247*
- Thoracic, right, and left cervical vagotomy (Reichsman), 600
- Thrombi, mural, endocardial and subendocardial degeneration, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Thrombocytopenic purpura, fatal, due to sodium salicylate, 242*
- Thromboembolic disease, venous, 521*
- Thromboplastic properties of some mercurial diuretics (Macht), 460
- Thromboses of thebesian veins, endocardial and subendocardial degeneration, and mural thrombi, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Time, prothrombin, in normal subjects and in patients with arteriosclerosis, study of (Meyers and Poindexter), 27
- relationships within cardiac cycle in electrocardiograms of normal men, analysis of (Schlamowitz), 329, 464, 473
- Tobacco, angina pectoris and, 525
- Toes, rate of blood flow in (Goetz), 158
- T-P interval, duration of, and its relationship to cycle length (R-R interval) (II); analysis of time relationships within cardiac cycle in electrocardiograms of normal men (Schlamowitz), 464
- Tracheal obstruction from vascular ring, surgical relief for, 113*
- Tracheobronchial tree, heart, and inferior vena cava of normal dogs, certain effects of positive pressure respiration on (Carr and Essex), 61
- Transfusion, blood, intracardiac, 385*
- Transient bundle branch block associated with tachycardia (Eichert), 511
- Transverse diameter of heart, method for orthodiagraphic measurement of, by means of simple fluoroscope (Howard), 724
- Trauma of limbs, acute hemorrhage or, effects of positive pressure respiration on circulation and respiration when combined with (Carr and Essex), 64
- vascular (II); surgical management of peripheral vascular disorders, 805*
- Traumatic shock in man, electrocardiograms in, 244*
- Tremor, circulation lying and standing, and bed exercises and early rising, studies of (I); convalescence from surgical procedures, 249*
- Tricuspid stenosis, congenital, 525
- Tsutsugamushi disease, cardiovascular disturbances in, 248*

- Shock, hemorrhagic, definition and criteria for its diagnosis, 660*
traumatic, in man, electrocardiograms in, 244*
- Shudder, carotid, 379*
- Sinoatrial, interatrial and, block, with illustrative case (Decherd et al.), 352
- Sinus arrhythmia and respiratory variation of ballistocardiogram, 659*
carotid, stimulation; hemiplegia following (Askey), 131
hyperactive carotid, reflex, angina pectoris, and myocardial infarction, case report of similar symptoms produced by (Glenn and Read), 792
- Size and shape of T wave, effect of exercise on (Dehn et al.), 188
- Skin and rectal temperatures, effect of splanchnic resection on peripheral blood flow and, in hypertension (Stewart et al.), 728
of lower extremities, rate and control of blood flow through (Goetz), 146
sensitivity, intolerance as shown by; mercurial diuretics, 378*
temperatures in hypertension, peripheral blood flow and (Stewart et al.), 617
- Smith, Fred M., 253
- Sodium restriction in diet for hypertension, 112*
salicylate, fatal thrombocytopenic purpura due to, 242*
treatment of acute rheumatic fever with large doses of, with special reference to dose management and toxic manifestations, 802*
- South Pacific malaria, experience with (Sprague), 428
- Sphygmomanometer, differences in blood pressure values determined by inflating and deflating cuff of (Cunningham), 220
- Spinal anesthesia, high, effect of, on blood pressure of patients with hypertension and far-advanced renal disease—its possible relationship to pathogenesis of hypertension (V); studies in hypertension, 379*
- Splanchnic resection, effect of, on peripheral blood flow and rectal and skin temperatures in hypertension (Stewart et al.), 728
- Stab wound of heart and pericardial effusion or empyema, pericardial tamponade from; study utilizing method of right heart catheterization (Warren et al.), 418
- Staphylococcus aureus septicemia and pericarditis treated with penicillin (Zimmerman and Durgin), 93
- Stenosis, congenital tricuspid, 525*
mitral, and arterial hypertension, 805*
pure congenital pulmonary (Freed and Budnitz), 369
- Stimulation, carotid sinus, hemiplegia following (Askey), 131
of cardiovascular receptors, paroxysmal pulmonary edema consequent to (Luisada and Sarnoff), 270, 282, 293
- Streptococcus, hemolytic, sore throat, abnormalities in electrocardiogram following, 658*
infection and rheumatic fever, some experimental aspects of, 110*
s.b.e. in subacute bacterial endocarditis, 383*
- Subendocardial and endocardial degeneration, mural thrombi, and thromboses of thebesian veins, presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
- Subjective sensations associated with extrasystoles, study of (Kline and Bidder), 254
- Sulfadiazine, prevention of rheumatic recurrences in children by use of, 379*
- Sulfathiazole, prevention of rheumatic recurrences in children by use of, 379*
- Surgical ablation of sinus node, three observations on chronic experimental nodal rhythm by, 804*
correction, experimental studies regarding; coarctation of aorta, 112*
for coarctation of aorta, 380*
ligation in patient with patent ductus arteriosus complicated by presence of multiple congenital cardiac defects, cure of subacute bacterial endarteritis by (Ziegler), 231
management of peripheral vascular disorders, 805**
procedures, convalescence from; I. Studies of circulation lying and standing, of tremor, and of program of bed exercises and early rising, 249*
II. Studies of various physiological responses to mild exercise test, 249*
relief for tracheal obstruction from vascular ring, 113*
therapy of patent ductus arteriosus, 110*
treatment, congenital coarctation of aorta and, 381*
consideration of two cardiac diseases amenable to, 243*
of arterial hypertension, 521*
of essential hypertensive cardiovascular disease in man, experiences with, 245*
physiopathology and, of congenital cardiovascular defects, 519*
- Sympathectomized extremities, blood flow in (Goetz), 168

Typhus fever, scrub, electrocardiographic changes in (Hollander), 481
 pathologic study of thirty-one cases of, with especial reference to cardiovascular system (Levine), 314

U

Unipolar derivation, critical study of, 108-
 Uremia, electrocardiographic changes in pericarditis associated with (Keith et al.), 527
 Urethane anesthesia, bilateral cervical vagotomy under (Reichsman), 599

V

Vagal pulmonocoronary reflex in pulmonary embolism? (Malinow et al.), 702
 Vagotomized rats, bilaterally, plasma and blood volume determination in (Reichsman), 605
 Vagotomy, bilateral cervical, and sympathectomy in rat under ether anesthesia (Reichsman), 595
 under urethane anesthesia (Reichsman), 599
 studies on pathogenesis of pulmonary edema following (Reichsman), 590
 right thoracic and left cervical (Reichsman), 600
 Valve, mitral, calcification of (Fertman and Wolff), 580
 Vascular disorders, peripheral, surgical management of, 805*
 II. Vascular trauma, 805*
 pattern, characteristic, in patients with rheumatoid arthritis, 380*
 ring, surgical relief for tracheal obstruction from, 113*
 Vectorcardiogram, method for construction of, from Einthoven electrocardiogram (Howard), 191
 Vein, great cardiac, treatment of coronary disease with angina by pericoronary neurectomy combined with ligation of (Fauteux), 260
 coronary, ligation of, in man (Fauteux), 261
 Veins, thebesian, thromboses of, endocardial and subendocardial degeneration, and mural thrombi. presence and pathogenesis of, in cardiac failure from causes other than myocardial infarction (Flynn and Mann), 757
 Vena cava, inferior, tracheobronchial tree, and heart, of normal dogs, effects of positive pressure respiration on (Carr and Essex), 61

Vena caval syndrome, superior; report of thirty-five cases (Hussey et al.), 1
 Venospasm, its part in producing clinical picture of Raynaud's disease, 521*

Venous filling, time of, 107*
 hypertension in man, normal venous pressure values and study of certain clinical aspects; use of phlebomanometer (Winsor and Burch), 387
 pressure, establishment of normal values for (Winsor and Burch), 395
 factors affecting (Winsor and Burch), 391
 in patients with right ventricular congestive heart failure (Winsor and Burch), 397
 pressures in disorders of venous system of lower extremities, 380*
 return, action of cardiac ejection on, 655*
 in absence of cardiac drive, 382*
 intra-abdominal pressure and regulation of, 107*
 thromboembolic disease, 521*
 Ventricle, cardiac, action of heat and cold on different components of electrogram of, 107*
 left, electrocardiographic effects of injury at endocardial surface of (Bayley), 677
 turtle, action of acetylcholine and epinephrine on, 381*
 Ventricular fibrillation (Parsonnet et al.), 769
 tachycardia, paroxysmal (Freudlich), 557
 treated with quinidine, 111*
 Veterans discharged because of heart disease or hypertension, re-examination of, 520*
 Vitamin P, observations on treatment of rheumatic fever with, 244*

W

Wolff-Parkinson-White syndrome and related problems, 108
 in association with congenital heart disease: coarctation of aorta (Bodlander), 785
 Wound, stab, of heart and pericardial effusion or empyema, pericardial tamponade from; study utilizing method of right heart catheterization (Warren et al.), 418
 Wounds, penetrating, of chest, circulation in; study by method of right heart catheterization (Merrill et al.), 413